NOVEL TAXANES AND METHODS RELATED TO USE AND PREPARATION THEREOF

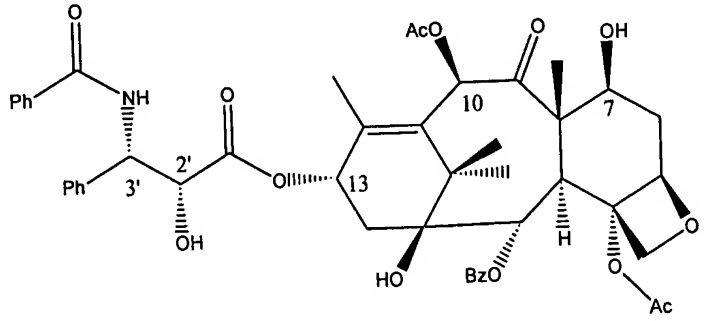
BACKGROUND OF THE INVENTION

Field of the Invention

The present invention relates generally to taxanes, compounds useful in the preparation of taxanes, and synthetic methods useful in the preparation of taxanes.

Description of the Related Art

The taxane family of terpenes has received much attention in the scientific and medical community because members of this family have demonstrated broad spectrum anti-leukemic and tumor-inhibitory activity. A well-known member of this family is paclitaxel, which has the following structure,



wherein Ac is acetyl, Bz is benzoyl, Ph is phenyl, the 2' position has the R configuration and the 3' position has the S configuration. Paclitaxel was first isolated from the bark of the pacific yew tree (*Taxus brevifolia*) in 1971, and has proved to be a potent natural anticancer agent. For example, paclitaxel has been found to have activity against different forms of leukemia and against solid tumors in the breast, ovary, brain, and lung in humans.

This activity has stimulated an intense research effort over recent years, including the search for other taxanes having similar or improved properties, and the development of synthetic pathways for making taxanes such as paclitaxel. One result from this research effort was the discovery of an analog of paclitaxel called taxotere. Taxotere has been found to have very good anti-tumor activity and better bio-availability than paclitaxel. Taxotere is similar in structure to paclitaxel, having t-butoxycarbonyl instead of benzoyl on the amino group at the 3' position, and a hydroxyl group instead of the acetoxy group at the C-10 position (see EP 253738 for a discussion of taxotere).

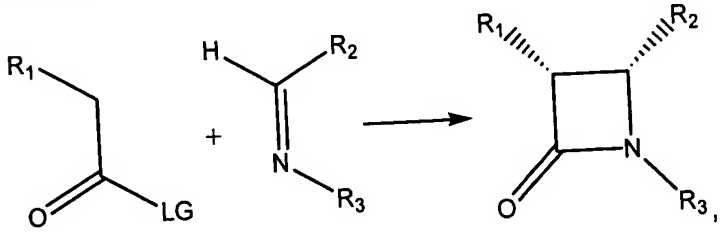
Taxanes are structurally complicated molecules, and the development of commercially viable synthetic methods to make taxanes has been a challenge. Semi-synthetic pathways have been developed, where these methods begin with the isolation of a naturally occurring material and then the conversion of that material to the taxane of interest. One such pathway for the semi-synthesis of paclitaxel begins with 10-deacetylbaccatin III, a taxane isolated from the needles of the English yew tree (*Taxus baccata*). A semi-synthetic route for the production of taxotere has been reported that involves coupling of N-tert-butoxycarbonyl-(2R, 3S)-3-phenylisoserine with 10-deacetylbaccatin III in conjunction with proper protecting groups (*Tetrahedron Letters* 33:5185, 1992). The synthesis of taxotere has also been reported using enantiomerically pure beta-lactams as intermediates (*J. Org. Chem.* 56:1681, 1991; *Tetrahedron* 48:6985, 1992).

While significant advances have been made in this field, there remain a need for improved synthetic techniques for the production of paclitaxel and analogs thereof such as taxotere. For example, existing semi-synthetic pathways for production of paclitaxel generally involve coupling of a suitable side chain precursor to the free hydroxyl group at position 13 of 10-deacetylbaccatin III. Fully synthetic pathways also employ addition of such side-chains in a similar way. Thus, there is a need for improved routes for the generation of such precursors of

the C-13 side chain, particularly since this side-chain has been found to be an important structural feature. The present invention fulfils these needs and provides other related advantages.

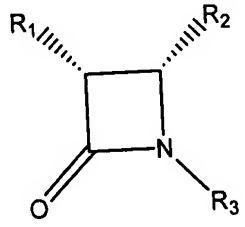
BRIEF SUMMARY OF THE INVENTION

In one aspect, the present invention provides a process of preparing a beta-lactam, where the process comprises the scheme



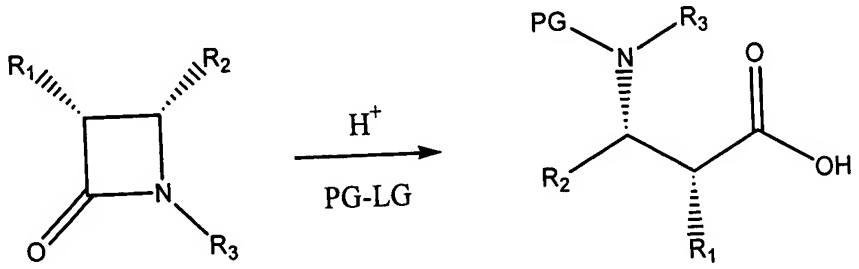
wherein R_1 is hydroxyl, protected hydroxyl, thiol, or protected thiol; LG is a leaving group; R_2 is alkyl, alkenyl, alkynyl, or aryl where R_2 is optionally substituted with one or more of halogen, hydroxyl, alkoxy, aryloxy, heteroaryloxy, amino, alkylamino, dialkylamino, mercapto, alkylthio, arylthio, heteroarylthio, cyano, carboxyl, alkoxycarbonyl where the alkoxy portion contains 1 to 15 carbons, aryloxycarbonyl where the aryloxy portion contains 6 to 20 carbon, or heteroarylcarbonyl where the heteroaryl portion contains 3 to 15 carbon atoms; and R_3 is hydrogen. Optionally, $(R_2)(H)C=N-R_3$ is prepared by reaction between an aldehyde of the formula R_2-CHO, and an amine of the formula R_3-NH_2. Also optionally, R_1 is phenyl and R_2 is phenyl.

In another aspect, the present invention provides a compound of the formula



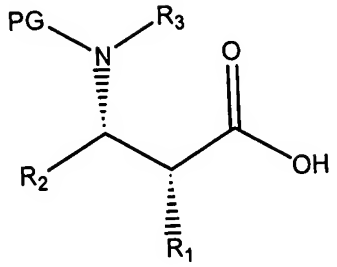
wherein R_1 is thiol (SH), tBOC, acetate, methoxy, thiophenyl, Cl_2CH-C(O)O- or 1-ethoxyethyl, R_2 is phenyl and R_3 is hydrogen, and salts thereof.

In another aspect, the present invention provides a process of opening a beta-lactam ring, where the process comprises the scheme



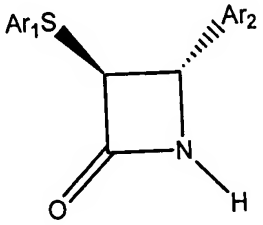
wherein R_1 is hydroxyl, protected hydroxyl, thiol, or protected thiol; LG is a leaving group; PG is an amine protecting group; R_2 is alkyl, alkenyl, alkynyl, or aryl where R_2 is optionally substituted with one or more of halogen, hydroxyl, alkoxy, aryloxy, heteroaryloxy, amino, alkylamino, dialkylamino, mercapto, alkylthio, arylthio, heteroarylthio, cyano, carboxyl, alkoxycarbonyl where the alkoxy portion contains 1 to 15 carbons, aryloxycarbonyl where the aryloxy portion contains 6 to 20 carbon, or heteroarylcarbonyl where the heteroaryl portion contains 3 to 15 carbon atoms; R_3 is hydrogen, C_1-C_6 alkyl or aryl where R_3 is optionally substituted with one or more halogens, hydroxyl, alkoxy, aryloxy, heteroaryloxy, amino, alkylamino, dialkylamino, mercapto, alkylthio, arylthio, heteroarylthio, cyano, carboxyl, alkoxycarbonyl where the alkoxy portion contains 1 to 15 carbons, aryloxycarbonyl where the aryloxy portion contains 6 to 20 carbon, or heteroarylcarbonyl where the heteroaryl portion contains 3 to 15 carbon atoms; and H^+ is a proton source.

In another aspect, the present invention provides an isoserine compound of the formula



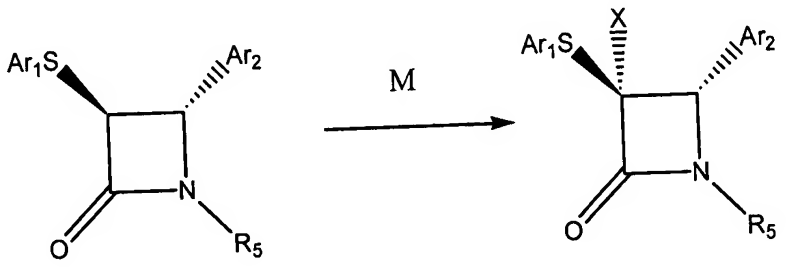
wherein R_1 is hydroxyl, protected hydroxyl, thiol, or protected thiol; PG is an amino protecting group; R_2 is alkyl, alkenyl, alkynyl, or aryl where R_2 is optionally substituted with one or more of halogen, hydroxyl, alkoxy, aryloxy, heteroaryloxy, amino, alkylamino, dialkylamino, mercapto, alkylthio, arylthio, heteroarylthio, cyano, carboxyl, alkoxycarbonyl where the alkoxy portion contains 1 to 15 carbons, aryloxycarbonyl where the aryloxy portion contains 6 to 20 carbon, or heteroarylcarbonyl where the heteroaryl portion contains 3 to 15 carbon atoms; R_3 is hydrogen, C_1-C_6 alkyl or aryl where R_3 is optionally substituted with one or more halogens, hydroxyl, alkoxy, aryloxy, heteroaryloxy, amino, alkylamino, dialkylamino, mercapto, alkylthio, arylthio, heteroarylthio, cyano, carboxyl, alkoxycarbonyl where the alkoxy portion contains 1 to 15 carbons, aryloxycarbonyl where the aryloxy portion contains 6 to 20 carbon, or heteroarylcarbonyl where the heteroaryl portion contains 3 to 15 carbon atoms; and salts and esters thereof.

In another aspect, the present invention provides a process of forming a beta lactam of the formula



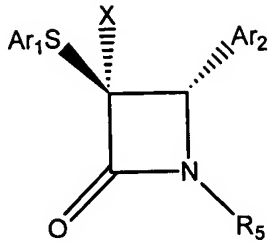
wherein Ar_1 and Ar_2 are each aryl groups, where each of Ar_1 and Ar_2 are independently optionally substituted with one or more of halogen, hydroxyl, alkoxy, aryloxy, heteroaryloxy, amino, alkylamino, dialkylamino, mercapto, alkylthio, arylthio, heteroarylthio, cyano, carboxyl, alkoxycarbonyl where the alkoxy portion contains 1 to 15 carbon atoms, and aryloxycarbonyl where the aryloxy portion contains 6 to 20 carbon atoms; and where the process comprises reacting together compounds of the formula $Ar_1S\text{-}CH_2\text{-}C(=O)Cl$, NH_3, and $Ar_2\text{-}CHO$ under conditions that form the beta lactam.

In another aspect, the present invention provides a process comprising the following scheme



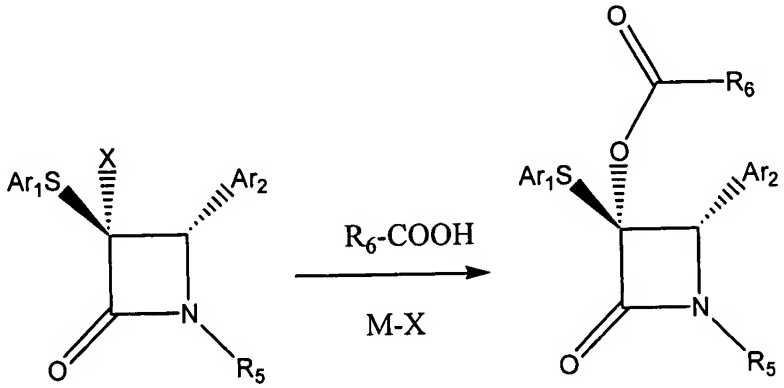
wherein Ar_1 and Ar_2 are each aryl groups, where each of Ar_1 and Ar_2 is independently optionally substituted with one or more of halogen, hydroxyl, alkoxy, aryloxy, heteroaryloxy, amino, alkylamino, dialkylamino, mercapto, alkylthio, arylthio, heteroarylthio, cyano, carboxyl, alkoxycarbonyl where the alkoxy portion contains 1 to 15 carbon atoms, and aryloxycarbonyl where the aryloxy portion contains 6 to 20 carbon atoms; X is halide; R_5 is selected from hydrogen, benzoyl and tBOC, and M is a halogenating agent.

In another aspect, the present invention provides a compound of the formula



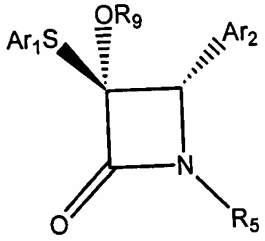
wherein Ar_1 and Ar_2 are each aryl groups, where each of Ar_1 and Ar_2 are independently optionally substituted with one or more of halogen, hydroxyl, alkoxy, aryloxy, heteroaryloxy, amino, alkylamino, dialkylamino, mercapto, alkylthio, arylthio, heteroarylthio, cyano, carboxyl, alkoxycarbonyl where the alkoxy portion contains 1 to 15 carbon atoms, and aryloxycarbonyl where the aryloxy portion contains 6 to 20 carbon atoms; X is halide; and R_5 is selected from hydrogen, benzoyl tBOC, C_1-C_6 alkyl or aryl where R_5 is optionally substituted with one or more halogens, hydroxyl, alkoxy, aryloxy, heteroaryloxy, amino, alkylamino, dialkylamino, mercapto, alkylthio, arylthio, heteroarylthio, cyano, carboxyl, alkoxycarbonyl where the alkoxy portion contains 1 to 15 carbons, aryloxycarbonyl where the aryloxy portion contains 6 to 20 carbon, or heteroarylcarbonyl where the heteroaryl portion contains 3 to 15 carbon atoms, and salts thereof.

In another aspect, the present invention provides a process comprising the scheme



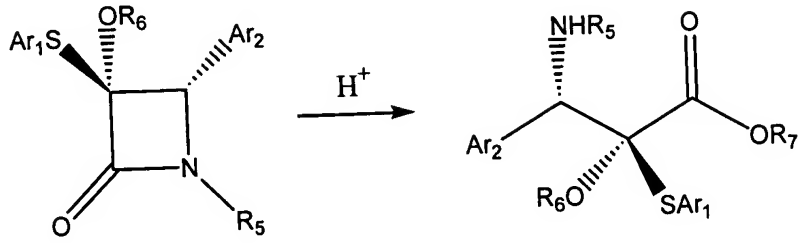
wherein Ar_1 and Ar_2 are each aryl groups, where each of Ar_1 and Ar_2 are independently optionally substituted with one or more of halogen, hydroxyl, alkoxy, aryloxy, heteroaryloxy, amino, alkylamino, dialkylamino, mercapto, alkylthio, arylthio, heteroarylthio, cyano, carboxyl, alkoxycarbonyl where the alkoxy portion contains 1 to 15 carbon atoms, and aryloxycarbonyl where the aryloxy portion contains 6 to 20 carbon atoms; M is metal and X is one or more halides attached to the metal; R_5 is selected from hydrogen, benzoyl and tBOC; and R_6 is C_1-C_6 alkyl.

In another aspect, the present invention provides a compound of the formula



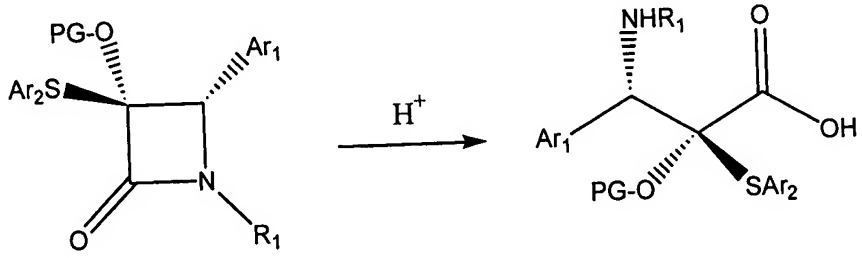
wherein Ar_1 and Ar_2 are each aryl groups, where each of Ar_1 and Ar_2 are independently optionally substituted with one or more of halogen, hydroxyl, alkoxy, aryloxy, heteroaryloxy, amino, alkylamino, dialkylamino, mercapto, alkylthio, arylthio, heteroarylthio, cyano, carboxyl, alkoxycarbonyl where the alkoxy portion contains 1 to 15 carbon atoms, and aryloxycarbonyl where the aryloxy portion contains 6 to 20 carbon atoms; R_5 is selected from hydrogen, benzoyl and tBOC; and R_9 is a hydroxyl protecting group. Optionally, R_9 is selected from methoxymethyl, methoxyethyl, 1-ethoxyethyl, benzyloxymethyl, (beta-trimethylsilyl-ethoxy)methyl, tetrahydropyranyl, 2,2,2-trichloro-ethoxycarbonyl, benzyloxycarbonyl, *tert*-butoxycarbonyl, 9-fluorenylmethoxycarbonyl, 2,2,2-trichloroethoxymethyl, trimethylsilyl, triethylsilyl, tripropylsilyl, dimethylethylsilyl, dimethyl(t-butyl)silyl, diethylmethylsilyl, dimethylphenylsilyl, diphenylmethylsilyl, acetyl, chloroacetyl, dichloroacetyl, trichloroacetyl and trifluoroacetyl.

In another aspect, the present invention provides a process comprising the scheme



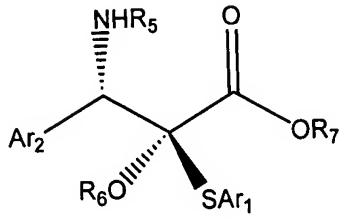
wherein Ar_1 and Ar_2 are aryl groups independently selected at each occurrence, R_5 is selected from hydrogen, benzoyl and tBOC, R_6 is a hydroxy protecting group, R_7 is hydrogen or C_1-C_6alkyl, and H+ represents a proton source, *e.g.*, an organic acid or mineral acid.

In another aspect, the present invention provides a process of opening a beta lactam according to the scheme



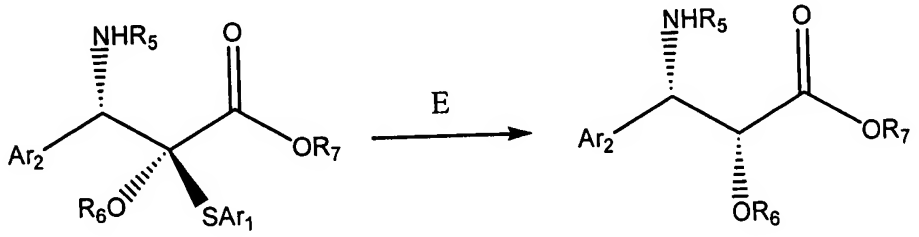
wherein PG is a hydroxyl protecting group; Ar_1 and Ar_2 are each aryl groups, where each of Ar_1 and Ar_2 are independently optionally substituted with one or more of halogen, hydroxyl, alkoxy, aryloxy, heteroaryloxy, amino, alkylamino, dialkylamino, mercapto, alkylthio, arylthio, heteroarylthio, cyano, carboxyl, alkoxycarbonyl where the alkoxy portion contains 1 to 15 carbon atoms, and aryloxycarbonyl where the aryloxy portion contains 6 to 20 carbon atoms; R_1 is hydrogen, alkyl, or –O-PG wherein PG is a protecting group, and H+ represents a proton source, *e.g.*, organic or mineral acid.

In another aspect, the present invention provides a compound of the formula



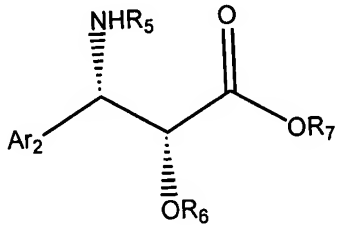
wherein Ar_1 and Ar_2 are each aryl groups, where each of Ar_1 and Ar_2 is independently optionally substituted with one or more of halogen, hydroxyl, alkoxy, aryloxy, heteroaryloxy, amino, alkylamino, dialkylamino, mercapto, alkylthio, arylthio, heteroarylthio, cyano, carboxyl, alkoxycarbonyl where the alkoxy portion contains 1 to 15 carbon atoms, and aryloxycarbonyl where the aryloxy portion contains 6 to 20 carbon atoms; R_5 is selected from hydrogen, benzoyl and tBOC; R_6 is a hydroxyl protecting group, and R_7 is hydrogen or C_1-C_6alkyl. Optionally, R_6 is selected from methoxymethyl, methoxyethyl, 1-ethoxyethyl, benzyloxymethyl, (beta-trimethylsilyl-ethoxy)methyl, tetrahydropyranyl, 2,2,2-trichloro-ethoxycarbonyl, benzyloxycarbonyl, *tert*-butoxycarbonyl, 9-fluorenylmethoxycarbonyl, 2,2,2-trichloroethoxymethyl, trimethylsilyl, triethylsilyl, tripropylsilyl, dimethylethylsilyl, dimethyl(t-butyl)silyl, diethylmethylsilyl, dimethylphenylsilyl, diphenylmethylsilyl, acetyl, chloroacetyl, dichloroacetyl, trichloroacetyl and trifluoroacetyl.

In another aspect, the present invention provides a process comprising the scheme



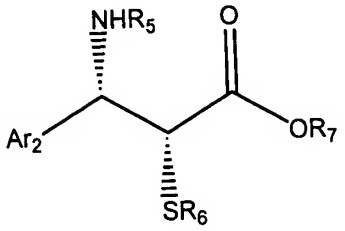
wherein Ar_1 and Ar_2 are each aryl groups, where each of Ar_1 and Ar_2 is independently optionally substituted with one or more of halogen, hydroxyl, alkoxy, aryloxy, heteroaryloxy, amino, alkylamino, dialkylamino, mercapto, alkylthio, arylthio, heteroarylthio, cyano, carboxyl, alkoxycarbonyl where the alkoxy portion contains 1 to 15 carbon atoms, and aryloxycarbonyl where the aryloxy portion contains 6 to 20 carbon atoms; R_5 is selected from hydrogen, benzoyl and tBOC, R_6 is C_1-C_6 alkyl, R_7 is H or C_1-C_6 alkyl, and E represents a desulfuration reagent.

In another aspect, the present invention provides a compound of the formula



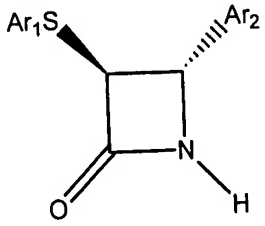
wherein Ar_2 is an aryl group optionally substituted with one or more of halogen, hydroxyl, alkoxy, aryloxy, heteroaryloxy, amino, alkylamino, dialkylamino, mercapto, alkylthio, arylthio, heteroarylthio, cyano, carboxyl, alkoxycarbonyl where the alkoxy portion contains 1 to 15 carbon atoms, and aryloxycarbonyl where the aryloxy portion contains 6 to 20 carbon atoms; R_5 is selected from hydrogen, benzoyl and tBOC; R_6 is a hydroxyl protecting group, and R_7 is H or C_1-C_6 alkyl. Optional hydroxyl protecting groups for R_6 include, without limitation, methoxymethyl, methoxyethyl, 1-ethoxyethyl, benzyloxymethyl, (beta-trimethylsilyl-ethoxy)methyl, tetrahydropyranyl, 2,2,2-trichloro-ethoxycarbonyl, benzyloxycarbonyl, *tert*-butoxycarbonyl, 9-fluorenylmethoxycarbonyl, 2,2,2-trichloroethoxymethyl, trimethylsilyl, triethylsilyl, tripropylsilyl, dimethylethylsilyl, dimethyl(t-butyl)silyl, diethylmethylsilyl, dimethylphenylsilyl, diphenylmethylsilyl, acetyl, chloroacetyl, dichloroacetyl, trichloroacetyl and trifluoroacetyl.

In another aspect, the present invention provides a compound of the formula

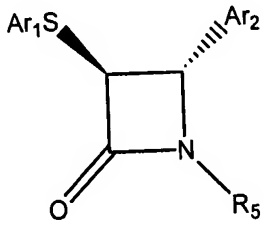


wherein Ar_2 is an aryl group optionally substituted with one or more of halogen, hydroxyl, alkoxy, aryloxy, heteroaryloxy, amino, alkylamino, dialkylamino, mercapto, alkylthio, arylthio, heteroarylthio, cyano, carboxyl, alkoxycarbonyl where the alkoxy portion contains 1 to 15 carbon atoms, and aryloxycarbonyl where the aryloxy portion contains 6 to 20 carbon atoms; R_5 is selected from hydrogen, benzoyl and tBOC, R_6 is a thiol protecting group, and R_7 is H or C_1-C_6 alkyl.

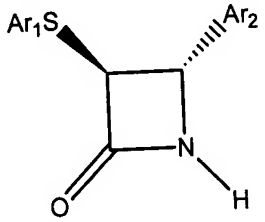
In another aspect, the present invention provides a process of substituting the nitrogen of a beta lactam, comprising treating a beta lactam of the structure



with a base and a protecting agent, to provide a beta lactam of the structure

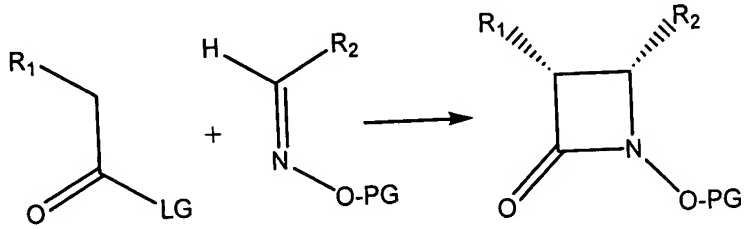


wherein Ar_1 and Ar_2 are each aryl groups, where each of Ar_1 and Ar_2 is independently optionally substituted with one or more of halogen, hydroxyl, alkoxy, aryloxy, heteroaryloxy, amino, alkylamino, dialkylamino, mercapto, alkylthio, arylthio, heteroarylthio, cyano, carboxyl, alkoxycarbonyl where the alkoxy portion contains 1 to 15 carbon atoms, and aryloxycarbonyl where the aryloxy portion contains 6 to 20 carbon atoms; and R_5 is selected from benzoyl and tBOC. Optionally, the protecting agent is benzoyl chloride or di-tert-butyl-dicarbonate. Optionally, this process is preceeded by forming a beta lactam of the formula



by a process comprising reacting together compounds of the formula $Ar_1S\text{-}CH_2\text{-}C(=O)Cl$, base, and $Ar_2\text{-}CHO$ under conditions that form the beta lactam. Optionally, the base is ammonia.

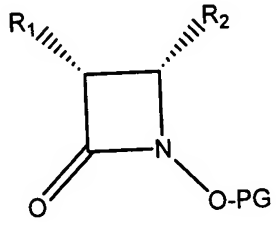
In another aspect, the present invention provides a process for preparing a beta lactam, comprising the scheme



wherein R_1 is hydroxyl, protected hydroxyl, thiol, or protected thiol; LG is a leaving group; R_2 is alkyl, alkenyl, alkynyl or aryl, where R_2 may be optionally substituted with one or more of halogen, hydroxyl, alkoxy, aryloxy, heteroaryloxy, amino, alkylamino, dialkylamino, mercapto, alkylthio, arylthio, heteroarylthio, cyano, carboxyl, alkoxycarbonyl where the alkoxy portion contains 1 to 15 carbons, aryloxycarbonyl where the aryloxy portion contains 6 to 20 carbon, or

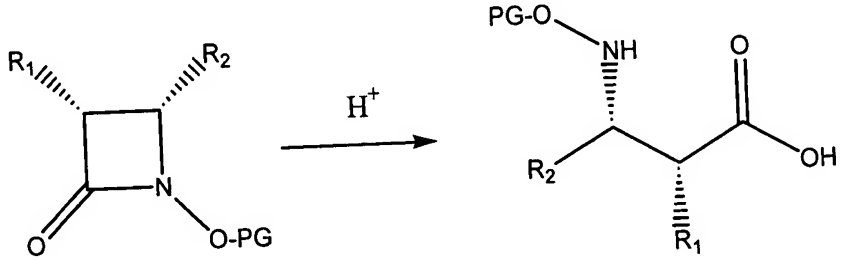
heteroarylcarbonyl where the heteroaryl portion contains 3 to 15 carbon atoms; and PG is a protecting group.

In another aspect, the present invention provides a compound of the formula



wherein R_1 is hydroxyl, protected hydroxyl, thiol, or protected thiol; R_2 is alkyl, alkenyl, alkynyl or aryl, where R_2 may be optionally substituted with one or more of halogen, hydroxyl, alkoxy, aryloxy, heteroaryloxy, amino, alkylamino, dialkylamino, mercapto, alkylthio, arylthio, heteroarylthio, cyano, carboxyl, alkoxycarbonyl where the alkoxy portion contains 1 to 15 carbons, aryloxycarbonyl where the aryloxy portion contains 6 to 20 carbon, or heteroarylcarbonyl where the heteroaryl portion contains 3 to 15 carbon atoms; and PG is a protecting group.

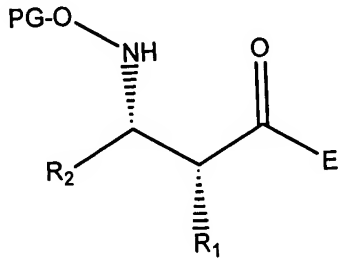
In another aspect, the present invention provides a process comprising the scheme



wherein R_1 is hydroxyl, protected hydroxyl, thiol, or protected thiol; R_2 is alkyl, alkenyl, alkynyl or aryl, where R_2 may be optionally substituted with one or more of halogen, hydroxyl, alkoxy, aryloxy, heteroaryloxy, amino, alkylamino, dialkylamino, mercapto, alkylthio, arylthio, heteroarylthio, cyano, carboxyl, alkoxycarbonyl where the alkoxy portion contains 1 to 15 carbons, aryloxycarbonyl where the aryloxy

portion contains 6 to 20 carbon, or heteroarylcarbonyl where the heteroaryl portion contains 3 to 15 carbon atoms; and PG is a protecting group, where H+ represents a proton source such as organic or mineral acid.

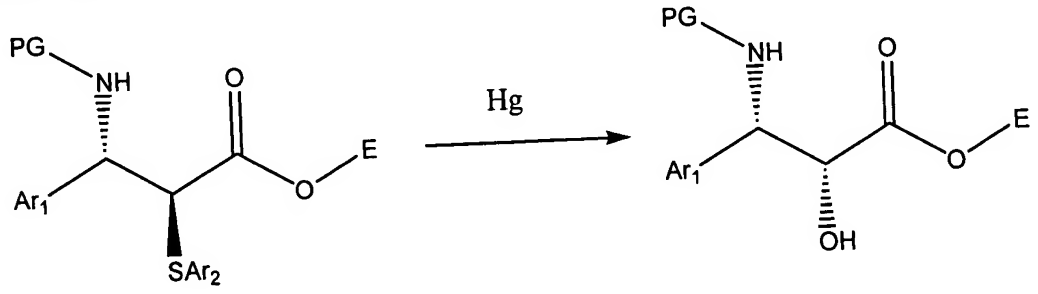
In another aspect, the present invention provides a compound of the formula



wherein R_1 is hydroxyl, protected hydroxyl, thiol, protected thiol, alkyl, alkenyl, alkynyl, or aryl where R_1 is optionally substituted with one or more of halogen, hydroxyl, alkoxy, aryloxy, heteroaryloxy, amino, alkylamino, dialkylamino, mercapto, alkylthio, arylthio, heteroarylthio, cyano, carboxyl, alkoxycarbonyl where the alkoxy portion contains 1 to 15 carbons, aryloxycarbonyl where the aryloxy portion contains 6 to 20 carbon, or heteroarylcarbonyl where the heteroaryl portion contains 3 to 15 carbon atoms; R_2 is alkyl, alkenyl, alkynyl or aryl, where R_2 may be optionally substituted with one or more of halogen, hydroxyl, alkoxy, aryloxy, heteroaryloxy, amino, alkylamino, dialkylamino, mercapto, alkylthio, arylthio, heteroarylthio, cyano, carboxyl, alkoxycarbonyl where the alkoxy portion contains 1 to 15 carbons, aryloxycarbonyl where the aryloxy portion contains 6 to 20 carbon, or heteroarylcarbonyl where the heteroaryl portion contains 3 to 15 carbon atoms; PG is a protecting group; and salts and esters thereof. Optionally, R_1 is selected from methoxymethyl, methoxyethyl, 1-ethoxyethyl, benzyloxymethyl, (beta-trimethylsilyl-ethoxy)methyl, tetrahydropyranyl, 2,2,2-trichloro-ethoxycarbonyl, benzyloxycarbonyl, *tert*-butoxycarbonyl, 9-fluorenylmethoxycarbonyl, 2,2,2-trichloroethoxymethyl, trimethylsilyl, triethylsilyl, tripropylsilyl, dimethylethylsilyl,

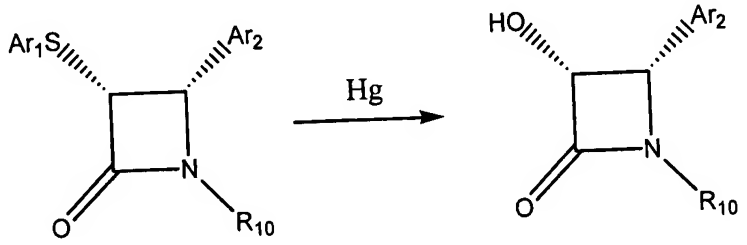
dimethyl(t-butyl)silyl, diethylmethylsilyl, dimethylphenylsilyl, diphenylmethylsilyl, acetyl, chloroacetyl, dichloroacetyl, trichloroacetyl and trifluoroacetyl.

In another aspect, the present invention provides a process of replacing a thioaryl group with a hydroxyl group according to the scheme



wherein PG is an amine protecting group, Ar_1 and Ar_2 are each aryl groups, where each of Ar_1 and Ar_2 is independently optionally substituted with one or more of halogen, hydroxyl, alkoxy, aryloxy, heteroaryloxy, amino, alkylamino, dialkylamino, mercapto, alkylthio, arylthio, heteroarylthio, cyano, carboxyl, alkoxycarbonyl where the alkoxy portion contains 1 to 15 carbon atoms, and aryloxycarbonyl where the aryloxy portion contains 6 to 20 carbon atoms; E is hydrogen or an organic group, and Hg represents a mercury-containing oxidizing agent. Optionaly, PG is benzoyl or tBOC; optionally, E is hydrogen; optionally, Ar_1 and Ar_2 are each phenyl; and optionally Hg is HgO or $Hg(CF_3CO_2)_2$.

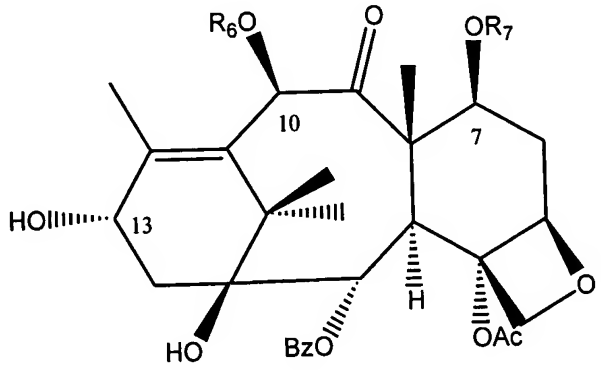
In another aspect, the present invention provides a process of replacing a thioaryl group with a hydroxyl group according to the following scheme



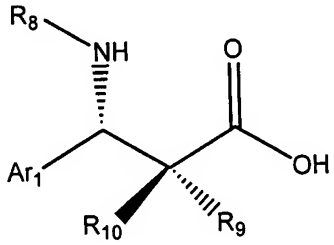
wherein Hg represents a mercuric reagent, and Ar_1 and Ar_2 are independently selected from alkyl, alkenyl, alkynyl, aryl or substituted aryl radical; and R_{10} is hydrogen, C_1-C_6alkyl, aryl or substituted aryl radical; wherein a substituted aryl

radical is substituted with one or more of halogen, hydroxyl, alkoxy, aryloxy, heteroaryloxy, amino, alkylamino, dialkylamino, mercapto, alkylthio, arylthio, heteroarylthio, cyano, carboxyl, alkoxycarbonyl where the alkoxy portion contains 1 to 15 carbons, aryloxycarbonyl where the aryloxy portion contains 6 to 20 carbon, or heteroarylcarbonyl where the heteroaryl portion contains 3 to 15 carbon atoms. Exemplary mercuric reagents are mercuric oxide and mercuric trifluoroacetate. Optionally, the process is conducted with the addition of ceric ammonium nitrate (CAN).

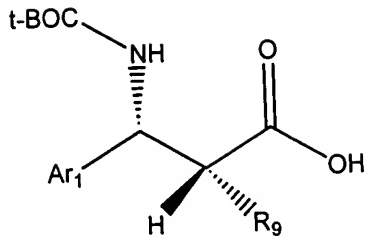
In another aspect, the present invention provides a process comprising esterifying a compound of the formula



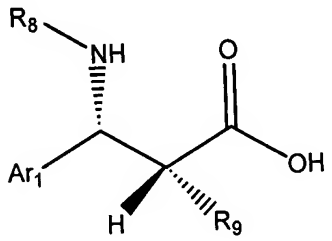
wherein R_6 is acetyl or dichloroacetyl; and R_7 is triethylsilyl, dichloroacetyl or 2,2,2-trichloroethoxycarbonyl (Troc); with an acid compound of a formula selected from



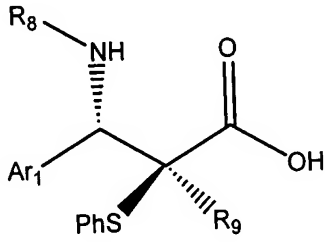
wherein R_8 is tBOC, PMP, Bz or H; R_9 is thiophenyl, acetoxy, methoxy, t-butoxycarbonyloxy, phenoxy, ethoxyethyl, or dichloroacetyl; and R_{10} is hydrogen. Optionally, the acid compound has the formula



wherein Ar_1 is phenyl and R_9 is thiophenyl, acetoxy, methoxy, t-butoxycarbonyloxy, phenoxy, ethoxyethyl, or dichloroacetyl. As another option, the acid compound has the formula

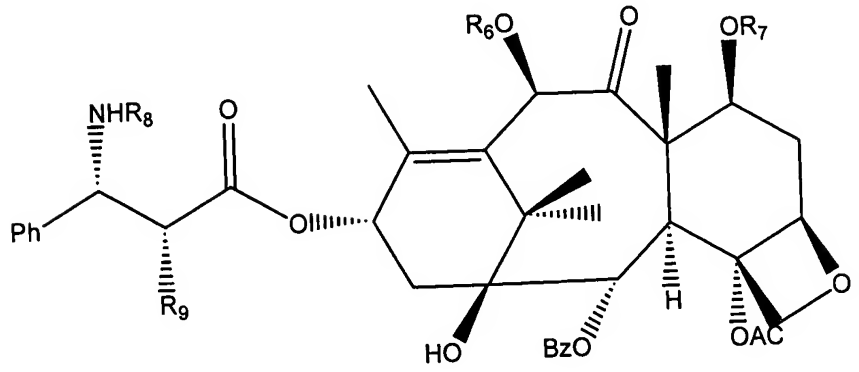


wherein Ar_1 is phenyl, R_8 is tBOC, PMP or H, and R_9 is acetoxy. As another option, the acid compound has the formula



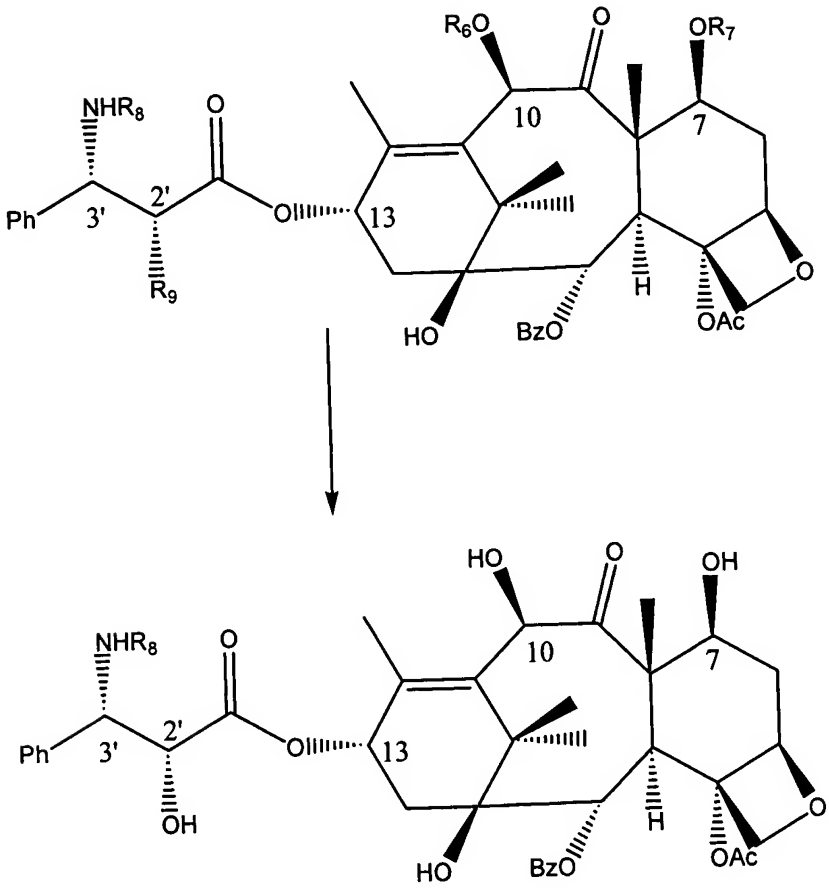
wherein Ar_1 is phenyl, R_8 is hydrogen or PMP, and R_9 is acetoxy, methoxy, t-butoxycarbonyloxy, phenoxy, ethoxyethyl, or dichloroacetyl.

In another aspect, the present invention provides a compound of the formula

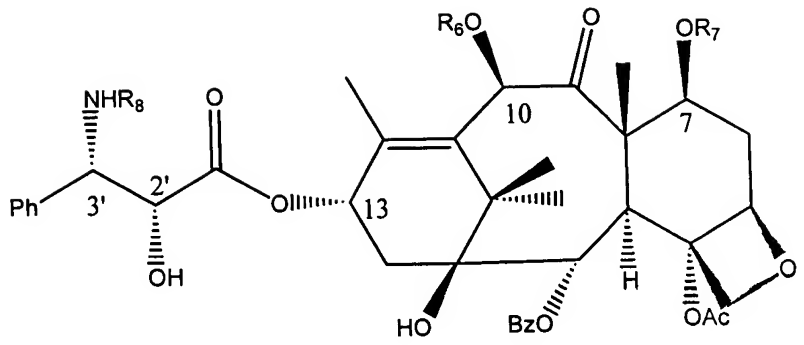


wherein R_6 and R_7 are independently selected from hydrogen, triethylsilyl, acetyl and dichloroacetyl, with the proviso that R_6 and R_7 may not be simultaneously hydrogen, R_8 is tBOC, PMP, Bz or H, and R_9 is thiophenyl, acetoxy, methoxy, t-butoxycarbonyloxy, ethoxyethyl, or dichloroacetyl. Optionally, R_6 and R_7 are each dichloroacetyl; R_8 is tBOC; and R_9 is thiophenyl, acetoxy, methoxy, t-butoxycarbonyloxy, ethoxyethyl, or dichloroacetyl. As another option, R_6 is acetyl, R_7 is –TES, R_8 is t-BOC, and R_9 is thiophenyl, acetoxy, methoxy, t-butoxycarbonyloxy, or dichloroacetoxy. As yet another option, R_6 and R_7 are each dichloroacetyl, R_8 is tBOC, PMP or H, and R_9 is acetoxy. One additional option is that R_6 is acetyl, R_7 is triethylsilyl, R_8 is tBOC, PMP, Bz or H, and R_9 is acetoxy, where these options are exemplary options.

In another aspect, the present invention provides a process comprising the scheme

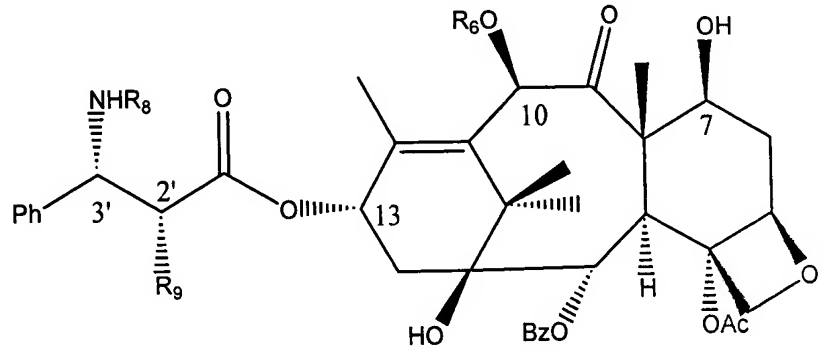


wherein R_6 and R_7 are independently selected from hydrogen, triethylsilyl, acetyl and dichloroacetyl, with the proviso that R_6 and R_7 may not be simultaneously hydrogen, R_8 is tBOC, PMP, Bz or H, and R_9 is thiophenyl, acetoxy, methoxy, t-butoxycarbonyloxy, ethoxyethyl, or dichloroacetyl. Optionally, the compound of structure (I) is deprotected at the 2' position to form an intermediate of structure (Ia), and the intermediate is treated with zinc acetate dihydrate to form the compound of formula (II), where the intermediate has the structure



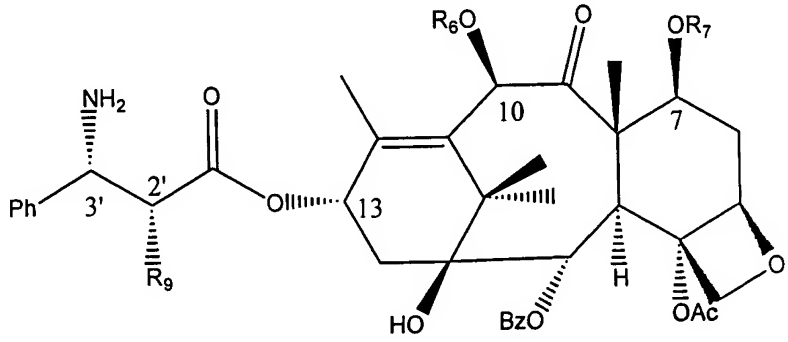
(Ia)

Also optionally, the compound of formula (I) is treated with protic acid and tertiary amine in an organic solvent to form an intermediate of formula (Ib), and the intermediate is deprotected at the 2' position to form the compound of formula (II), where the intermediate has the structure



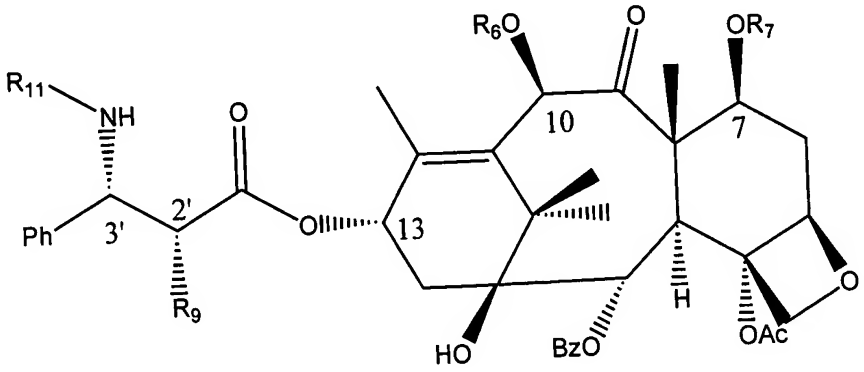
(Ib)

In another aspect, the present invention provides a method of preparing TAXOTERE, comprising reacting a compound of structure (III) with t-BOC, followed by deprotection of at least one of the 2', 7 and 10 positions, where the compound of structure (III) is



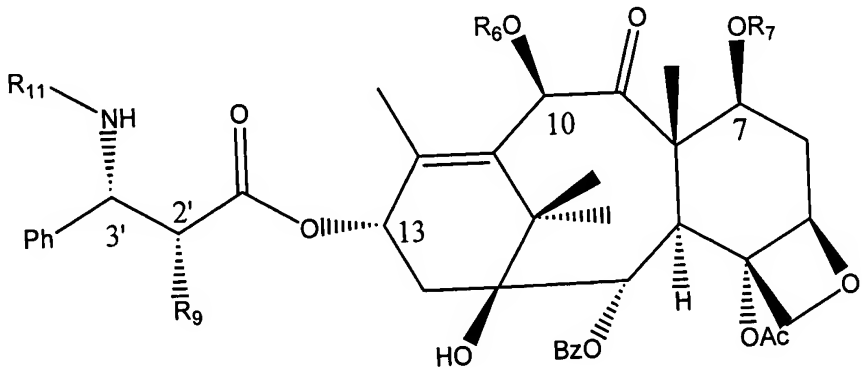
(III)

wherein R_6 and R_7 are independently selected from hydrogen, triethylsilyl, acetyl, Troc and dichloroacetyl, with the proviso that R_6 and R_7 may not be simultaneously hydrogen, and R_9 is thiophenyl, acetoxy, methoxy, t-butoxycarbonyloxy, or dichloroacetyl or ethoxyethyl. Optionally, R_6 and R_7 are each dichloroacetyl and R_9 is acetoxy. Also optionally, the compound of structure (III) is prepared by the reduction of a compound of structure (IV)



(IV)

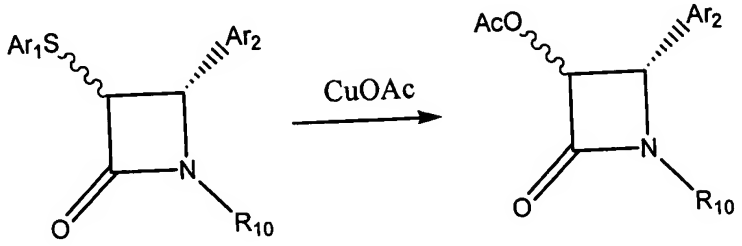
wherein R_6 and R_7 are each dichloroacetyl, R_9 is acetoxy, and R_{11} is OCO-t-Bu. In a preferred embodiment, R_6 is acetyl or dichloroacetyl, R_7 is TES or Troc, and R_9 is acetoxy or ethoxyethyl. In one option, the compound of structure (III) is prepared by the reduction of a compound of structure (IV)



(IV)

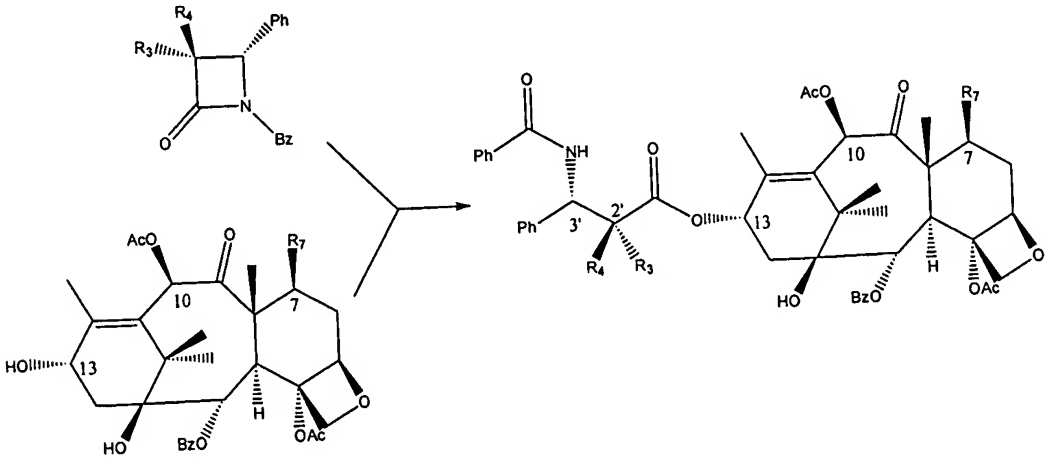
wherein R_6 is Ac, R_7 is TES, R_9 is acetoxy, and R_{11} is PMP, OCOO-t-Bu or H.

In another aspect, the present invention provides a process comprising the scheme



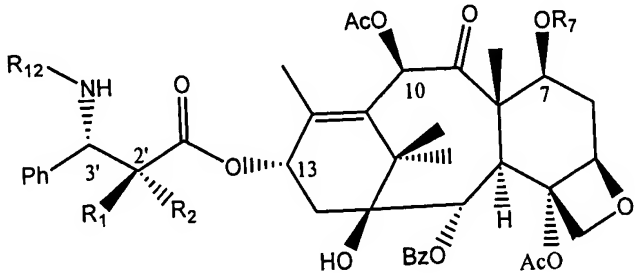
wherein Ar_1 and Ar_2 are independently selected from alkyl, alkenyl, alkynyl, aryl or substituted aryl radical; and R_{10} is hydrogen, C_1-C_6alkyl, aryl or substituted aryl radical; where a substituted aryl radical is substituted with one or more of halogen, hydroxyl, alkoxy, aryloxy, heteroaryloxy, amino, alkylamino, dialkylamino, mercapto, alkylthio, arylthio, heteroarylthio, cyano, carboxyl, alkoxycarbonyl where the alkoxy portion contains 1 to 15 carbons, aryloxycarbonyl where the aryloxy portion contains 6 to 20 carbon, or heteroarylcarbonyl where the heteroaryl portion contains 3 to 15 carbon atoms. The wavy line from Ar_1S to the ring indicates that both the alpha and beta forms are included.

In another aspect, the present invention provides a process of coupling a beta lactam to a baccatin III compound according to the following scheme

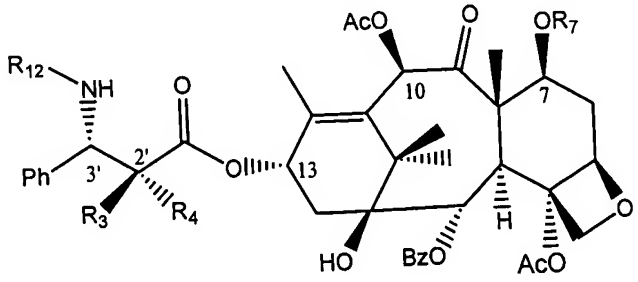


wherein R_3 and R_4 are independently selected from hydrogen, hydroxyl, protected hydroxyl, thiol, protected thiol, alkyl, alkenyl, alkynyl, or aryl where R_3 and R_4 are optionally substituted with one or more of halogen, hydroxyl, alkoxy, aryloxy, heteroaryloxy, amino, alkylamino, dialkylamino, mercapto, alkylthio, arylthio, heteroarylthio, cyano, carboxyl, alkoxycarbonyl where the alkoxy portion contains 1 to 15 carbons, aryloxycarbonyl where the aryloxy portion contains 6 to 20 carbon, or heteroarylcarbonyl where the heteroaryl portion contains 3 to 15 carbon atoms; R_7 is hydroxyl or a protected hydroxyl group; and the coupling is performed by addition of metal hydride, metal alkoxide or lewis acid to the reaction mixture.

In another aspect, the present invention provides a process for making a compound of formulas (III') or (IV'):

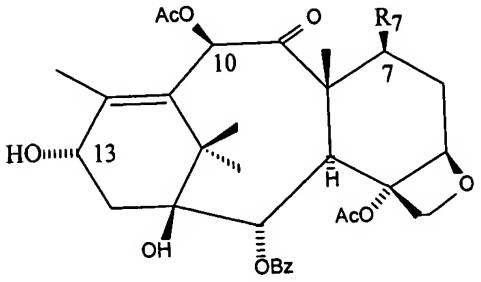


(III')



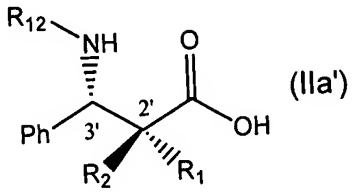
(IV')

comprising the step of reacting a compound of formula (I')

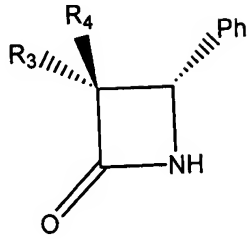


(I')

with a compound of formula (IIa') or (IIb')



(IIa')



(IIb')

wherein R_1, R_2, R_3 and R_4 are independently selected from hydrogen, hydroxyl, protected hydroxyl, thiol, protected thiol, alkyl, alkenyl, alkynyl, or aryl where R_1 and R_3 are optionally substituted with one or more of halogen, hydroxyl, alkoxy, aryloxy, heteroaryloxy, amino, alkylamino, dialkylamino, mercapto, alkylthio, arylthio, heteroarylthio, cyano, carboxyl, alkoxycarbonyl where the alkoxy portion contains 1 to 15 carbons, aryloxycarbonyl where the aryloxy portion contains 6 to 20 carbon, or heteroarylcarbonyl where the heteroaryl portion contains 3 to 15 carbon atoms; R_7 = -OCOCHCl$_2$, triethylsilyl or Troc; and R_{12} is an amine protecting group.

These and other aspects of this invention will be evident upon reference to the following detailed description.

BRIEF DESCRIPTION OF THE FIGURES

Figure 1 illustrates several chemical routes for the preparation of beta-lactam and phenylisoserine sidechains according to the present invention.

Figure 2 illustrates a chemical route for the preparation of beta-lactam and phenylisoserine sidechains according to the present invention.

Figure 3 illustrates a chemical route for the preparation of a beta-lactam and phenylisoserine sidechain according to the present invention.

Figure 4 illustrates chemical routes for the preparation of taxotere from various intermediate compounds prepared according to the present invention.

Figure 5 illustrates chemical routes for the preparation of taxotere from various intermediate compound prepared according to the present invention.

DETAILED DESCRIPTION OF THE INVENTION

In brief, the present invention relates to 3-phenylisoserine compounds as well as the preparation thereof and the intermediates formed during their preparation; baccatin III compounds and the preparation thereof; methods of joining together a 3-phenylisoserine compound and a baccatin III compound as well as the resulting chemical structure(s); and the conversion of one taxane compound to another taxane compound as well as the resulting chemical structure(s). Before providing a detailed description of these and other aspects of the present invention, the following list of definitions is provided to assist the reader in understanding the invention.

A. Definitions

The term "hydroxy-protecting group" refers to a readily cleavable group bonded to the oxygen of a hydroxyl (-OH) group. Examples of hydroxy protecting groups include, without limitation, acetyl (Ac), benzyl ($PhCH_2$), 1-ethoxyethyl (EE), methoxymethyl (MOM), (methoxyethoxy)methyl (MEM), (p-methoxyphenyl)methoxymethyl (MPM), tert-butyldimethylsilyl (TBS), tert-butyldiphenylsilyl (TBPS), tert-butoxycarbonyl (tBoc, t-Boc, tBOC, t-BOC), tetrahydropyranyl (THP), triphenylmethyl (Trityl, Tr), 2-methoxy-2-methylpropyl, benzyloxycarbonyl (Cbz), trichloroacetyl ($OCCCl_3$), 2,2,2-trichloroethoxycarbonyl

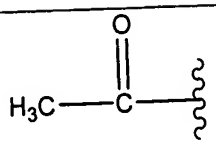
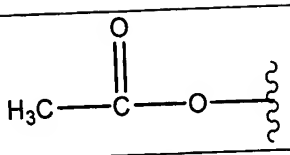
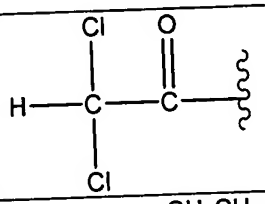
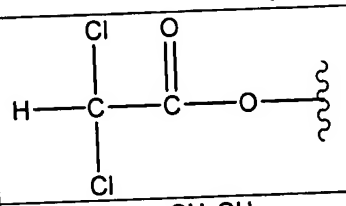
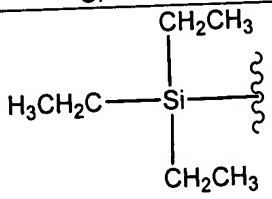
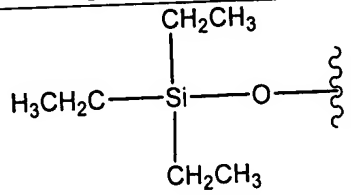
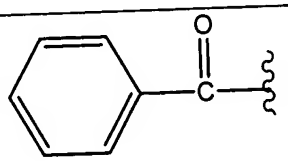
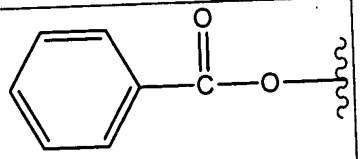
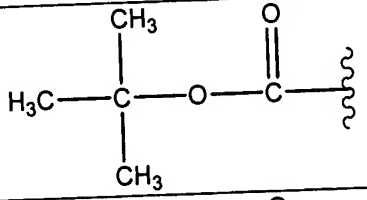
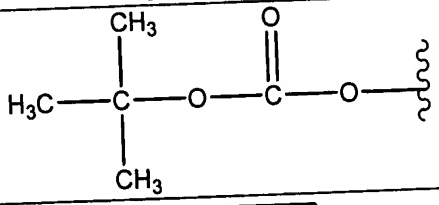
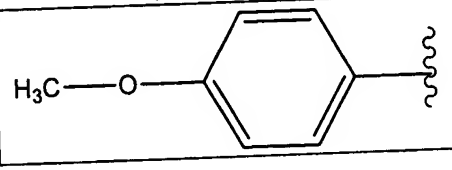
(Troc), benzyloxymethyl (BOM), tert-butyl (t-Bu), triethylsilyl (TES), trimethylsilyl (TMS), and triisopropylsilyl (TIPS). The related term "protected hydroxy group" refers to a hydroxy group that is bonded to a hydroxy-protecting group. General examples of protected hydroxy groups include, without limitation, -O-alkyl, -O-acyl, acetal, and -O-ethoxyethyl, where some specific protected hydroxy groups include, formyloxy, acetoxy, propionyloxy, chloroacetoxy, bromoacetoxy, dichloroacetoxy, trichloroacetoxy, trifluoroacetoxy, methoxyacetoxy, phenoxyacetoxy, benzoyloxy, benzoylformoxy, p-nitro benzoyloxy, ethoxycarbonyloxy, methoxycarbonyloxy, propoxycarbonyloxy, 2,2,2-trichloro ethoxycarbonyloxy, benzyloxycarbonyloxy, tert.-butoxycarbonyloxy, 1-cyclopropyl ethoxycarbonyloxy, phthaloyloxy, butyryloxy, isobutyryloxy, valeryloxy, isovaleryloxy, oxalyoxy, succinyloxy and pivaloyloxy, phenylacetoxy, phenylpropionyloxy, mesyloxy, chlorobenzoyloxy, para-nitrobenzoyloxy, para-tert-butyl benzoyloxy, capryloyloxy, acryloyloxy, methylcarbamoyloxy, phenylcarbamoyloxy, naphthylcarbamoyloxy, and the like. Hydroxy protecting groups and protected hydroxy groups are described in, *e.g.*, C. B. Reese and E. Haslam, "Protective Groups in Organic Chemistry," J. G. W. McOmie, Ed., Plenum Press, New York, N.Y., 1973, Chapters 3 and 4, respectively, and T. W. Greene and P. G. M. Wuts, "Protective Groups in Organic Synthesis," Second Edition, John Wiley and Sons, New York, N.Y., 1991, Chapters 2 and 3.

The term "thiol-protecting group" refers to a readily cleavable group bonded to the sulfur of a thiol (-SH) group. Examples of thiol protecting groups include, without limitation, triphenylmethyl (trityl, Trt), acetamidomethyl (Acm), benzamidomethyl, 1-ethoxyethyl, benzoyl, and the like. The related term "protected thiol group" refers to a thiol group that is bonded to a thiol-protecting group. General examples of protected thiol groups include, without limitation, -S-alkyl (alkylthio, e.g., C_1-C_{10}alkylthio), -S-acyl (acylthio), thioacetal, -S-aralkyl (aralkylthio, *e.g.*, aryl(C_1-C_4)alkylthio), where some specific protected thiols groups include methylthio, ethylthio, propylthio, isopropylthio, butylthio, isobutylthio, sec-

butylthio, tert-butylthio, pentylthio, isopentylthio, neopentylthio, hexylthio, heptylthio, nonylthio, cyclobutylthio, cyclopentylthio and cyclohexylthio, benzylthio, phenethylthio, propionylthio, n-butyrylthio and iso-butyrylthio. Thio protecting groups and protected thio groups are described in, *e.g.*, C. B. Reese and E. Haslam, "Protective Groups in Organic Chemistry," J. G. W. McOmie, Ed., Plenum Press, New York, N.Y., 1973, Chapters 3 and 4, respectively, and T. W. Greene and P. G. M. Wuts, "Protective Groups in Organic Synthesis," Second Edition, John Wiley and Sons, New York, N.Y., 1991, Chapters 2 and 3.

The term "amine protecting group" refers to groups known in the art that can be used to protect an amine group from undergoing an undesired chemical reaction. Examples of amine protecting groups include, but are not limited to: acyl types such as formyl, trifluoroacetyl, phthalyl, and p-toluenesulfonyl; aromatic carbamate types such as benzyloxycarbonyl (Cbz) and substituted benzyloxy-carbonyls, 1-(p-biphenyl)-1-methylethoxy-carbonyl, and 9-fluorenylmethyloxycarbonyl (Fmoc); aliphatic carbamate types such as tert-butyloxycarbonyl (tBoc), ethoxycarbonyl, diisopropylmethoxycarbonyl, and allyloxycarbonyl; cyclic alkyl carbamate types such as cyclopentyloxycarbonyl and adamantyloxycarbonyl; alkyl types such as triphenylmethyl and benzyl; trialkylsilane such as trimethylsilane; and thiol containing types such as phenylthiocarbonyl and dithiasuccinoyl. Amine protecting groups and protected amine groups are described in, *e.g.*, C. B. Reese and E. Haslam, "Protective Groups in Organic Chemistry," J. G. W. McOmie, Ed., Plenum Press, New York, N.Y., 1973, Chapters 3 and 4, respectively, and T. W. Greene and P. G. M. Wuts, "Protective Groups in Organic Synthesis," Second Edition, John Wiley and Sons, New York, N.Y., 1991, Chapters 2 and 3.

The following Table shows the chemical structure of some protecting groups, as well as nomenclature used to identify those chemical structures.

Acetyl (Ac)		Acetoxy (-OAc)	
Dichloroacetyl		Dichloroacetoxy	
Triethylsilyl (TES)		Triethylsiloxy (-OTES)	
Benzoyl		Benzoyloxy	
t-Butyloxycarbonyl (tBOC)			
t-Butoxycarbonyloxy (-O-tBOC)			
para-Methoxyphenyl (PMP)			

The term "alkyl" refers to a hydrocarbon structure wherein the carbons are arranged in a linear, branched, or cyclic manner, including combinations thereof. Lower alkyl refers to alkyl groups of from 1 to 5 carbon atoms. Examples of lower alkyl groups include methyl, ethyl, propyl, isopropyl,

butyl, s- and t-butyl and the like. Preferred alkyl groups are those of C20 or below. More preferred alkyl groups are those of C13 or below. Cycloalkyl is a subset of alkyl and includes cyclic hydrocarbon groups of from 3 to 13 carbon atoms. Examples of cycloalkyl groups include cyclopropyl, cyclobutyl, cyclopentyl, norbornyl, adamantyl and the like. When an alkyl residue having a specific number of carbons is named, all geometric isomers having that number of carbons are intended to be encompassed; thus, for example, "butyl" is meant to include n-butyl, sec-butyl, isobutyl and t-butyl; "propyl" includes n-propyl and isopropyl.

The term "alkenyl" refers to an alkyl group having at least one site of unsaturation, *i.e.,* at least one double bond.

The term "alkynyl" refers to an alkyl group having at least one triple bond between adjacent carbon atoms.

The terms "alkoxy" and "alkoxyl" both refer to moieties of the formula -O-alkyl. Examples include methoxy, ethoxy, propoxy, isopropoxy, cyclopropyloxy, cyclohexyloxy and the like. Lower-alkoxy refers to groups containing one to four carbons. The analogous term "aryloxy" refers to moieties of the formula –O-aryl.

The term "acyl" refers to moieties of the formula –C(=O)-alkyl. One or more carbons in the acyl residue may be replaced by nitrogen, oxygen or sulfur as long as the point of attachment to the parent remains at the carbonyl. Examples include acetyl, benzoyl, propionyl, isobutyryl, t-butoxycarbonyl, benzyloxycarbonyl and the like. Lower-acyl refers to groups containing one to four carbons.

The term aryl refers to phenyl or naphthyl. Substituted aryl refers to mono- and poly- substituted phenyl or naphthyl. Exemplary subsituents for aryl include one or more of halogen, hydroxyl, alkoxy, aryloxy, heteroaryloxy, amino, alkylamino, dialkylamino, mercapto, alkylthio, arylthio, heteroarylthio, cyano, carboxyl, alkoxycarbonyl where the alkoxy portion contains 1 to 15 carbons, aryloxycarbonyl where the aryloxy portion contains 6 to 20 carbon, or heteroarylcarbonyl where the heteroaryl portion contains 3 to 15 carbon atoms.

The term "heteroaryl" refers to a 5- or 6-membered heteroaromatic ring containing 1-3 heteroatoms selected from O, N, or S; a bicyclic 9- or 10-membered heteroaromatic ring system containing 0-3 heteroatoms selected from O, N, or S; or a tricyclic 13- or 14-membered heteroaromatic ring system containing 0-3 heteroatoms selected from O, N, or S. Exemplary aromatic heterocyclic rings include, e.g., imidazole, pyridine, indole, thiophene, benzopyranone, thiazole, furan, benzimidazole, quinoline, isoquinoline, quinoxaline, pyrimidine, pyrazine, tetrazole and pyrazole.

The term "leaving group" (LG) refer to a chemical moiety that may be displaced during a substitution or elimination reaction. Exemplary leaving groups include halide (*e.g.*, bromide and chloride) and as tosyl.

The term "halogenating agent" refers to a chemical that may be added to a reaction mixture to cause the addition of a halide to a carbon of an organic molecule. Halogenating agents include, for example, inorganic acid halides, for example thionyl chloride, phosphorus trichloride, phosphorus tribromide, phosphoryl chloride trifluoromethanesulfonic acid, N-iodosuccinimide and phosphorus pentachloride. Other halogenating are known in the art. The reaction is conveniently carried out in the presence of an excess of the halogenating agent in the presence of a solvent or diluent such as, for example, a halogenated solvent such as methylene chloride, chloroform or carbon tetrachloride. The reaction may conveniently carried out at a temperature in the range, for example, 10 to 150°C, preferably in the range 40 to 100°C.

In several instances, the present invention provides compounds including the designation "-CO_2-E" where E represents hydrogen or an organic group. In these instances, the compounds being disclosed are carboxylic acids or esters thereof. Optionally, E is hydrogen. Alternatively, E is an organic group, where preferred organic groups are alkyl, alkenyl, alkynyl, aryl, or heteroaryl as defined above. Optionally, E has a molecular weight of less than 1,000, preferably less than 500 g/mol.

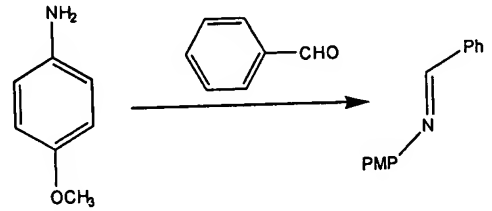
B. Sidechain Preparation

In various aspects, the present invention provides for the preparation of imine compounds, the conversion of an imine compound to a β-lactam compound, the preparation of oxime compounds, the conversion of an oxime compound to a β-lactam, the conversion of one β-lactam compound to another β-lactam compound, the ring-opening of a β-lactam compound to provide a 3-phenylisoserine compound, and the conversion of one 3-phenylisoserine compound to another 3-phenylisoserine compound. These various aspects of the invention are described in detail below. The individual reaction steps, the starting materials and products when novel, and sequences of reaction steps are all aspects of the present invention.

1. Preparation of imine compounds

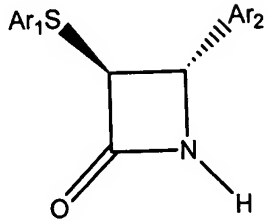
In one aspect of the invention, as illustrated in Reaction 1, the reaction of benzaldehyde with anisidine yields a *para*-methoxyphenyl (PMP)-protected imine.

Reaction 1



More specifically, to a solution of benzaldehyde in an inert solvent such as dichloromethane is added anisidine at about room temperature followed by magnesium sulfate and the reaction mixture stirred at room temperature for about 16 hours. The solid is filtered and the filtrate is evaporated to give the product imine.

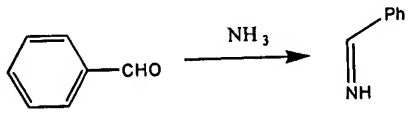
In another aspect, the present invention provides a process of forming a beta lactam of the formula



wherein Ar_1 and Ar_2 are each aryl groups, where each of Ar_1 and Ar_2 are independently optionally substituted with one or more of halogen, hydroxyl, alkoxy, aryloxy, heteroaryloxy, amino, alkylamino, dialkylamino, mercapto, alkylthio, arylthio, heteroarylthio, cyano, carboxyl, alkoxycarbonyl where the alkoxy portion contains 1 to 15 carbon atoms, and aryloxycarbonyl where the aryloxy portion contains 6 to 20 carbon atoms. The process comprises reacting together compounds of the formula Ar_1S-CH_2-C(=O)Cl, NH_3, and Ar_2-CHO under conditions that form the beta lactam. In one embodiment, each of Ar_1 and Ar_2 are phenyl.

For example, an aspect of the present invention is illustrated by Reaction 2, wherein an imine may be prepared by reacting benzaldehyde with ammonia.

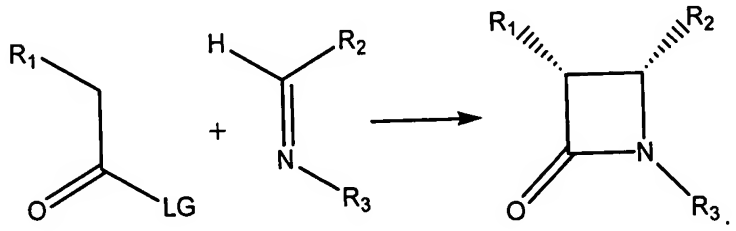
Reaction 2



More specifically, to a solution of benzaldehyde in a suitable solvent such as ethanol is added ammonia solution at room temperature, and the stirred reaction mixture is heated to about 40-50°C for about 2-3 hours. The resulting solid is filtered and washed with methanol or equivalent followed by water to give the imine.

2. Conversion of an imine compound to a beta-lactam compound

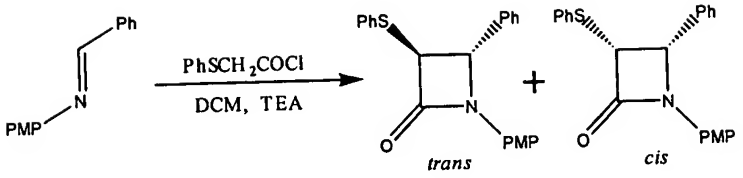
In one aspect, the present invention provides a process of preparing a beta-lactam, comprising the scheme



In this scheme, R_1 is hydroxyl, protected hydroxyl, thiol, or protected thiol; LG is a leaving group; R_2 is alkyl, alkenyl, alkynyl, or aryl where R_2 is optionally substituted with one or more of halogen, hydroxyl, alkoxy, aryloxy, heteroaryloxy, amino, alkylamino, dialkylamino, mercapto, alkylthio, arylthio, heteroarylthio, cyano, carboxyl, alkoxycarbonyl where the alkoxy portion contains 1 to 15 carbons, aryloxycarbonyl where the aryloxy portion contains 6 to 20 carbon, or heteroarylcarbonyl where the heteroaryl portion contains 3 to 15 carbon atoms; and R_3 is hydrogen. In a preferred embodiment, R_1 is thioaryl or substituted thioaryl, *e.g.*, thiophenyl or substituted thiophenyl. In one embodiment of the invention, R_1 is thiophenyl. In a preferred embodiment, R_2 is aryl or substituted aryl, *e.g.*, phenyl or substituted phenyl. In one embodiment of the invention, R_2 is phenyl. The scheme shows the formation of the cis product (*i.e.*, R_1 and R_2 are cis), however it is typically the case that both the cis and trans products are formed. As one option, the imine may be prepared as shown in Reaction 2, wherein $(R_2)(H)C=N-R_3$ is prepared by reaction between an aldehyde of the formula R_2-CHO, and an amine of the formula R_3-NH_2.

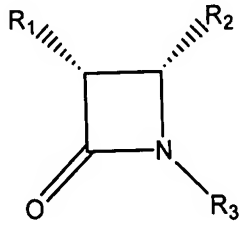
Reaction 3 shows a specific example of converting an imine to a β-lactam, where this specific conversion is another aspect of the present invention.

Reaction 3



More specifically, an imine is dissolved in an inert solvent such as dichloromethane and cooled to about 0°C under an inert atmosphere such as argon gas. Thiophenyl acetyl chloride or any other respective acid chloride is added dropwise to the cooled stirred solution of the imine at about 0°C. To the resulting solution is added dropwise a tertiary amine, *e.g.*, triethylamine, also at about 0°C. The reaction mixture is gradually warmed to room temperature and kept at this temperature for about 16 hours. The reaction is quenched by pouring into ice-cold water and extracted three times with dichloromethane and dried over anhydrous magnesium sulfate. The solvent is evaporated to give the crude product which is purified by column chromatography using dichloromethane initially followed by mixtures of hexane/ethyl acetate to get the pure cis and trans β-lactams shown in Reaction 3. The cis and trans isomers may be separated from one another by, *e.g.*, column chromatography. Either isomer, or the mixture of isomers, may be converted to a phenylisoserine compound as described later herein.

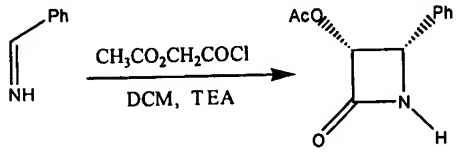
Thus, in another aspect, the present invention also provides compounds of the formula



wherein R_1 is thiol (SH), tBOC, acetate, methoxy, thiophenyl, Cl_2CH-C(O)O- or 1-ethoxyethyl, R_2 is phenyl and R_3 is hydrogen.

In another aspect of the invention, an imine without a protecting group attached to the imine nitrogen may be converted to a β-lactam as shown in Reaction 4, where this conversion is another aspect of the invention, and the chemical product is another aspect of the invention.

Reaction 4

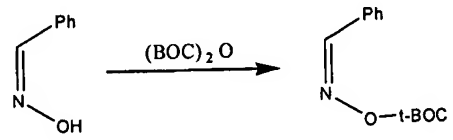


More specifically, to a stirred solution of an imine in an inert solvent such as anhydrous dichloromethane, and preferably under an inert atmosphere such as argon gas, is added acetoxy acetyl chloride dropwise at about 0°C. To this solution is added dropwise a tertiary amine, such as triethylamine, also at about 0°C. The reaction mixture is gradually warmed to room temperature and kept at this temperature for overnight. The reaction is quenched by pouring into ice-cold water and extracted three times with dichloromethane following by drying over anhydrous magnesium sulfate. The solvent is evaporated to give the crude product which may be purified by column chromatography using dichloromethane initially followed by mixtures of hexane/ethyl acetate to give the β-lactam.

3. Conversion of an oxime compound to a different oxime compound

In another aspect of the invention, an oxime compound is converted to a protected form as illustrated in Reaction 5.

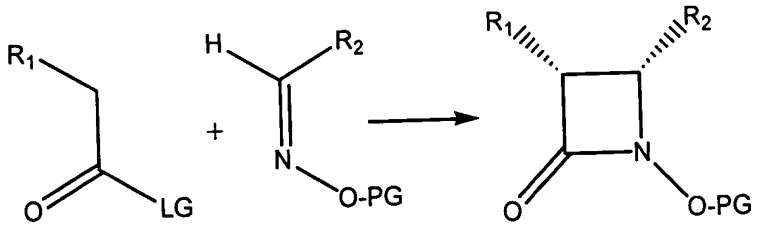
Reaction 5



More specifically, a syn-benzaldehyde oxime is added to a stirred solution of NaH in anhydrous THF at 0°C under an argon atmosphere. The reaction mixture is stirred at this temperature for 20 minutes and then $(BOC)_2$ is added dropwise. The reaction is stirred at 0°C for 1 hr and worked up as usual. The crude product is purified by column chromatography using hexane/dichloromethane to afford the pure product.

4. Conversion of an oxime compound to a beta-lactam compound

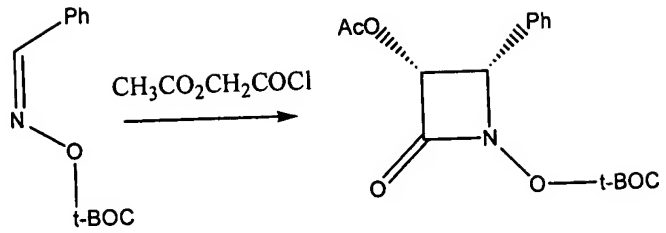
In another aspect the present invention provides a process for preparing a beta lactam, comprising the scheme



wherein R_1 is hydroxyl, protected hydroxyl, thiol, or protected thiol; LG is a leaving group; R_2 is alkyl, alkenyl, alkynyl or aryl, where R_2 may be optionally substituted with one or more of halogen, hydroxyl, alkoxy, aryloxy, heteroaryloxy, amino, alkylamino, dialkylamino, mercapto, alkylthio, arylthio, heteroarylthio, cyano, carboxyl, alkoxycarbonyl where the alkoxy portion contains 1 to 15 carbons, aryloxycarbonyl where the aryloxy portion contains 6 to 20 carbon, or heteroarylcarbonyl where the heteroaryl portion contains 3 to 15 carbon atoms; and PG is a protecting group. Noteworthy is that this process provides beta-lactam compounds having –O-PG substitution at the heterocyclic nitrogen ring.

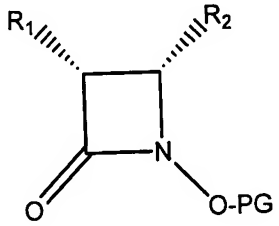
As an example, in one aspect of the invention, an oxime compound is converted to a beta-lactam having oxygen substitution on the ring nitrogen, as shown in Reaction 6.

Reaction 6



More specifically, a protected oxime is dissolved in dichloromethane and cooled to 0°C under argon atmosphere. Acetoxy acetyl chloride or any other acid chloride is added dropwise to the cooled stirred solution of the oxime at 0°C. To this solution is added dropwise DMAP or any other base also at 0°C. The reaction mixture is gradually warmed to room temperature (or may be heated to about 40°C) and keep at this temperature for 16 hours. The reaction is quenched by pouring into ice-cold water and extracted three times with dichloromethane and dried over anhydrous magnesium sulfate. The solvent is evaporated to give the crude product which is purified by column chromatography using dichloromethane initially followed by mixtures of hexane/ethyl acetate to get the pure product.

Thus, in a related aspect, the present invention provides compounds of the formula



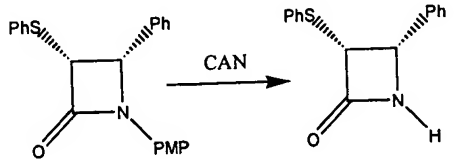
wherein R_1 is hydroxyl, protected hydroxyl, thiol, or protected thiol; R_2 is alkyl, alkenyl, alkynyl or aryl, where R_2 may be optionally substituted with one or more of halogen, hydroxyl, alkoxy, aryloxy, heteroaryloxy, amino, alkylamino, dialkylamino, mercapto, alkylthio, arylthio, heteroarylthio, cyano, carboxyl, alkoxycarbonyl where the alkoxy portion contains 1 to 15 carbons, aryloxycarbonyl where the aryloxy portion contains 6 to 20 carbon, or heteroarylcarbonyl where the heteroaryl portion

contains 3 to 15 carbon atoms; and PG is a protecting group. Optionally, R_1 is a protected hydroxyl group and the protecting group is selected from methoxymethyl, methoxyethyl, 1-ethoxyethyl, benzyloxymethyl, (beta-trimethylsilyl-ethoxy)methyl, tetrahydropyranyl, 2,2,2-trichloro-ethoxycarbonyl, benzyloxycarbonyl, *tert*-butoxycarbonyl, 9-fluorenylmethoxycarbonyl, 2,2,2-trichloroethoxymethyl, trimethylsilyl, triethylsilyl, tripropylsilyl, dimethylethylsilyl, dimethyl(t-butyl)silyl, diethylmethylsilyl, dimethylphenylsilyl, diphenylmethylsilyl, acetyl, chloroacetyl, dichloroacetyl, trichloroacetyl and trifluoroacetyl. Optionally, R_1 is a protected thiol group, and the protecting group is selected from triphenylmethyl (trityl, Trt), acetamidomethyl (Acm), benzamidomethyl, 1-ethoxyethyl and benzoyl.

5. Conversion of a beta-lactam compound to a different beta-lactam compound

A thiophenyl-substituted β-lactam having a protecting group on the ring nitrogen may be deprotected as shown in Reaction 7, where this deprotection reaction is another aspect of the present invention.

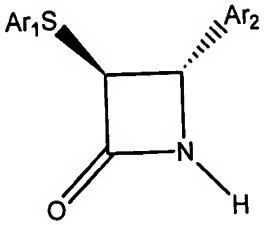
Reaction 7



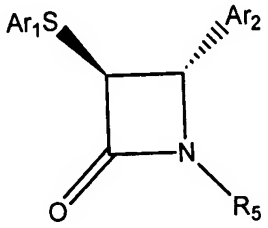
More specifically, cis beta lactam is dissolved in a suitable solvent such as acetonitrile under an inert atmosphere such as argon gas, and cooled to about 0°C. To this stirred cooled solution is added an aqueous solution of ceric ammonium nitrate (CAN) dropwise and the mixture is stirred for about 1 hour. The reaction mixture is poured into water and extracted three times with ethyl acetate. The combined organic phases are successively washed with (a) 5% sodium bicarbonate solution, (b) saturated sodium sulfate solution, and (c) saturated

sodium chloride solution, followed by drying over anhydrous sodium sulfite. After evaporation of the solvent under reduced pressure the crude product is purified by column chromatography twice using mixtures of hexane/ethyl acetate and dichloromethane/ethyl acetate to get the pure cis product. The same procedure could also be used to remove the paramethoxy group from trans β-lactam to give the corresponding 3-thiophenyl-azetidinone.

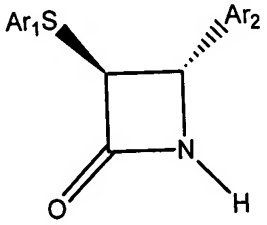
In another aspect, the present invention provides a process whereby the nitrogen atom of a beta-lactam is bonded to a protecting group. This aspect of the invention comprises treating a beta lactam of the structure



with a base and a protecting agent, to provide a beta lactam of the structure



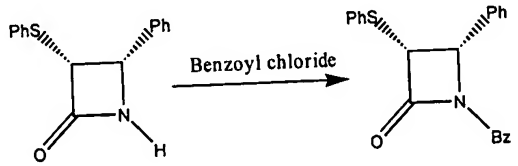
wherein Ar_1 and Ar_2 are aryl groups independently selected at each occurrence, and R_5 is selected from benzoyl and tBOC. The protecting agent may be, for example, benzoyl chloride or di-tert-butyl-dicarbonate. Optionally, this process is proceeded by forming a beta lactam of the formula



by a process comprising reacting together compounds of the formula $Ar_1S\text{-}CH_2\text{-}C(=O)Cl$, base, and $Ar_2\text{-}CHO$ under conditions that form the beta lactam. The base may be a nitrogen-containing base, *e.g.*, ammonia.

For example, the ring nitrogen of a β-lactam may be protected with an amine protecting group such as benzoyl (Bz, as shown in the following reaction) or t-BOC. This is illustrated in Reaction 8.

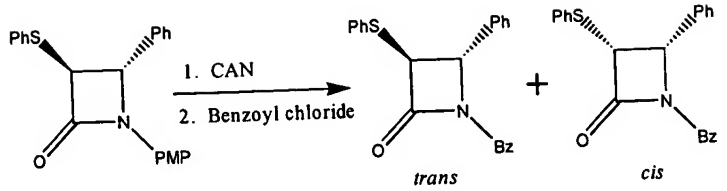
Reaction 8



More specifically, a β-lactam is dissolved in an inert solvent such as dichloromethane and cooled to ca. 0°C under an inert atmosphere, *e.g.*, argon gas. Dimethylaminopyridine (DMAP) and triethylamine are added followed by dropwise addition of benzoyl chloride at 0°C with stirring. The reaction mixture is stirred for about 1 hour and then was washed with saturated aqueous ammonium chloride and brine and dried over anhydrous sodium sulfate. After removal of the solvent under reduced pressure the crude product is purified by column chromatography using mixtures of dichloromethane/hexane to afford the pure benzoylated β-lactam.

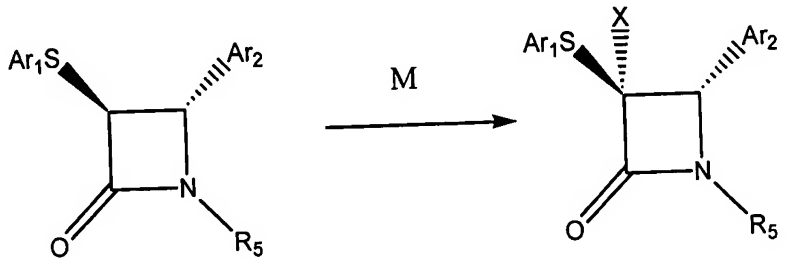
In another aspect of the invention, a paramethoxyphenyl protecting group attached to the ring nitrogen of a β-lactam is replaced with a benzoyl group as shown in Reaction 9.

Reaction 9



More specifically, the paramethoxy group of the trans β-lactam is removed by using ceric ammonium nitrate (CAN) in aqueous acetonitrile solution, followed by treating the product mixture with benzoyl chloride to afford a mixture of cis and trans benzoylated β-lactams.

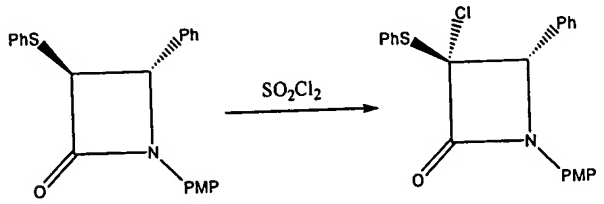
In another aspect, the present invention provides for the halogenation of a beta-lactam, as illustrated by the scheme



wherein Ar_1 and Ar_2 are each aryl groups, where each of Ar_1 and Ar_2 is independently optionally substituted with one or more of halogen, hydroxyl, alkoxy, aryloxy, heteroaryloxy, amino, alkylamino, dialkylamino, mercapto, alkylthio, arylthio, heteroarylthio, cyano, carboxyl, alkoxycarbonyl where the alkoxy portion contains 1 to 15 carbon atoms, and aryloxycarbonyl where the aryloxy portion contains 6 to 20 carbon atoms; X is halide; R_5 is selected from hydrogen, benzoyl and tBOC, and M is a halogenating agent. In one embodiment, each of Ar_1 and Ar_2 is phenyl. Exemplary halogenating agents include, without limitation, inorganic acid halides, for example thionyl chloride, phosphorus trichloride, phosphorus tribromide, phosphoryl chloride trifluoromethanesulfonic acid, N-iodosuccinimide and phosphorus pentachloride. In one embodiment of the invention, the halogenating agent is SO_2Cl_2.

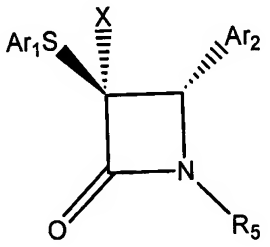
For example, a trans thiophenyl β-lactam can be modified by introducing a chloro group at the 3-position as shown in Reaction 10.

Reaction 10



More specifically, a trans thiophenyl beta lactam is dissolved in an inert solvent, *e.g.*, anhydrous dichloromethane, under an inert atmosphere, *e.g.*, argon gas, and cooled to about 0°C. Sulfuryl chloride is added dropwise to the stirred solution at ca. 0°C and left at this temperature for ca. 2 hrs. The solvent is evaporated and the residue dissolved in dichloromethane and washed successively with water, 10% sodium bicarbonate, saturated brine and dried over anhydrous sodium sulfate. After removal of the solvent under reduced pressure the crude solid is purified by recrystallization using mixtures of dichloromethane/hexanes to give the chloro group at the 3-position of the trans thiophenyl beta lactam.

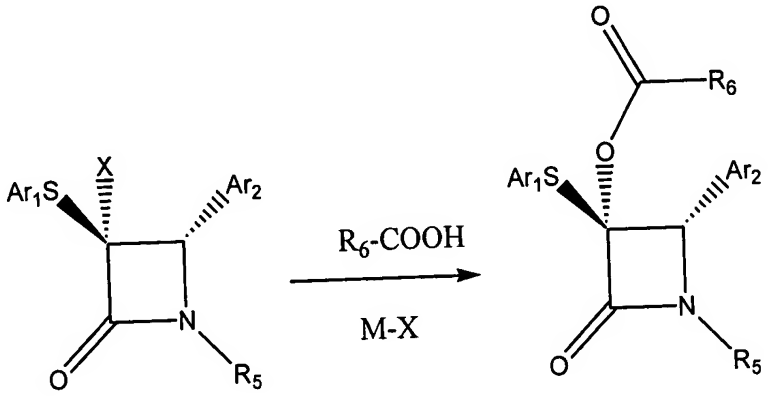
Thus, the present invention provides compounds of the formula



wherein Ar_1 and Ar_2 are each aryl groups, where each of Ar_1 and Ar_2 are independently optionally substituted with one or more of halogen, hydroxyl, alkoxy, aryloxy, heteroaryloxy, amino, alkylamino, dialkylamino, mercapto, alkylthio, arylthio, heteroarylthio, cyano, carboxyl, alkoxycarbonyl where the alkoxy portion contains 1 to 15 carbon atoms, and aryloxycarbonyl where the aryloxy

portion contains 6 to 20 carbon atoms; X is halide; and R_5 is selected from hydrogen, benzoyl, tBOC, C_1-C_6 alkyl or aryl where R_5 is optionally substituted with one or more halogens, hydroxyl, alkoxy, aryloxy, heteroaryloxy, amino, alkylamino, dialkylamino, mercapto, alkylthio, arylthio, heteroarylthio, cyano, carboxyl, alkoxycarbonyl where the alkoxy portion contains 1 to 15 carbons, aryloxycarbonyl where the aryloxy portion contains 6 to 20 carbon, or heteroarylcarbonyl where the heteroaryl portion contains 3 to 15 carbon atoms. For example, the invention provides compounds wherein Ar_1 and Ar_2 are each phenyl, X is chloride or bromide; and R_5 is hydrogen, benzoyl or tBOC.

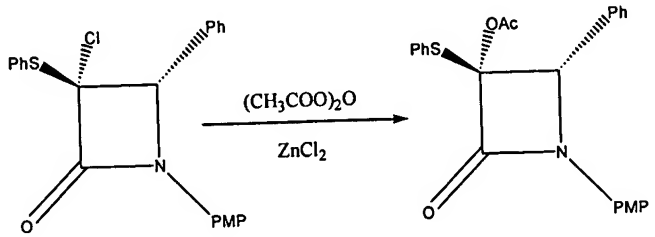
In another aspect, the present invention provides a process wherein a halide substituent on a beta-lactam ring is replaced with a protected hydroxyl group, as illustrated by the following scheme



wherein Ar_1 and Ar_2 are each aryl groups, where each of Ar_1 and Ar_2 are independently optionally substituted with one or more of halogen, hydroxyl, alkoxy, aryloxy, heteroaryloxy, amino, alkylamino, dialkylamino, mercapto, alkylthio, arylthio, heteroarylthio, cyano, carboxyl, alkoxycarbonyl where the alkoxy portion contains 1 to 15 carbon atoms, and aryloxycarbonyl where the aryloxy portion contains 6 to 20 carbon atoms; M is metal and X is one or more halides attached to the metal; R_5 is selected from hydrogen, benzoyl and tBOC; and R_6 is C_1-C_6 alkyl. In one exemplary embodiment of this aspect of the invention, Ar_1 and Ar_2 are each phenyl.

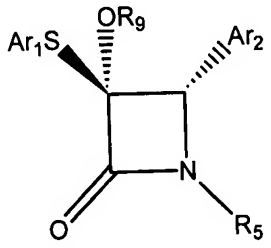
For instance, the present invention provides that a chloro-substituted beta-lactam may be converted into the corresponding beta-lactam where the chloride group is replaced with an acetate group. This conversion is illustrated in Reaction 11.

Reaction 11



More specifically, the chloro-substituted beta-lactam is dissolved in an inert solvent, *e.g.*, anhydrous dichloromethane, at room temperature under an inert atmosphere, *e.g.*, argon atmosphere. To this stirred solution at room temperature is added sequentially silica gel, zinc chloride and an alkyl anhydride, *e.g.*, acetic anhydride as shown in reaction XIIb. The reaction mixture is left at this temperature for ca. 16 hrs and then worked up. The silica gel is filtered and the filtrate evaporated, dissolved in dichloromethane and worked up as usual for this type of reaction. The crude residue is purified by column chromatography using mixtures of hexanes/ethyl acetate to afford the pure product.

Thus, the present invention provides compounds of the formula

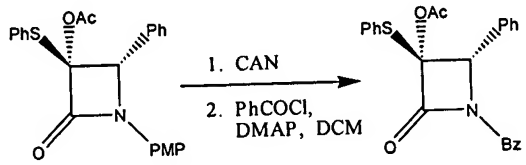


wherein Ar_1 and Ar_2 are each aryl groups, where each of Ar_1 and Ar_2 are independently optionally substituted with one or more of halogen, hydroxyl, alkoxy,

aryloxy, heteroaryloxy, amino, alkylamino, dialkylamino, mercapto, alkylthio, arylthio, heteroarylthio, cyano, carboxyl, alkoxycarbonyl where the alkoxy portion contains 1 to 15 carbon atoms, and aryloxycarbonyl where the aryloxy portion contains 6 to 20 carbon atoms; R_5 is selected from hydrogen, benzoyl and tBOC; and R_9 is a hydroxyl protecting group. For instance, in one aspect R_9 is selected from methoxymethyl, methoxyethyl, 1-ethoxyethyl, benzyloxymethyl, (beta-trimethylsilyl-ethoxy)methyl, tetrahydropyranyl, 2,2,2-trichloro-ethoxycarbonyl, benzyloxycarbonyl, *tert*-butoxycarbonyl, 9-fluorenylmethoxycarbonyl, 2,2,2-trichloroethoxymethyl, trimethylsilyl, triethylsilyl, tripropylsilyl, dimethylethylsilyl, dimethyl(t-butyl)silyl, diethylmethylsilyl, dimethylphenylsilyl, diphenylmethylsilyl, acetyl, chloroacetyl, dichloroacetyl, trichloroacetyl and trifluoroacetyl. Alternatively, or in addition, in another aspect Ar_1 and Ar_2 are each phenyl.

In another aspect of the invention, the protecting group of an N-protected beta lactam is replaced with a different protecting group, as shown in Reaction 12.

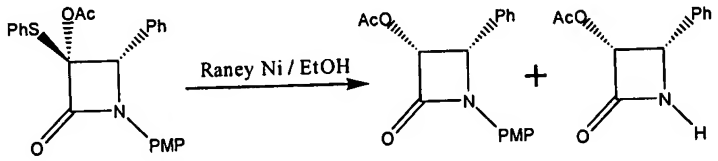
Reaction 12



More specifically, a paramethoxyphenyl (PMP) group is cleaved by using the procedure as in Reaction 7. The product obtained from this cleavage is dissolved in an inert solvent, *e.g.*, anhydrous dichloromethane, at ca. room temperature under argon atmosphere. To this stirred solution is added DMAP and dropwise benzoyl chloride, and the reaction is maintained at this temperature for about 1.5 hrs. The reaction mixture is worked up as usual and purified by column chromatography using mixtures of hexanes/ethyl acetate to afford the pure benzoylated beta lactam

In another aspect of the invention, the thiophenyl group of a thiophenyl-substituted beta lactam is removed using a desulfurization reagent, and a hydrogen put in its place. An example is shown in Reaction 13, where the desulfurization reagent is Raney Ni.

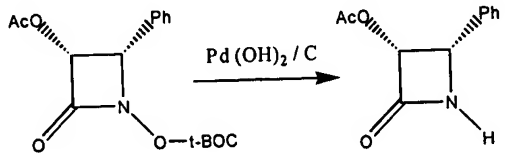
Reaction 13



In one specific example, a thiophenyl-substituted beta lactam is dissolved in ethanol at room temperature and Raney nickel is added in one portion to the stirred solution and the reaction mixture is stirred at this temperature for about 2 hrs. The reaction mixture is filtered and the filtrate is evaporated. The residue is dissolved in an inert solvent such as dichloromethane and worked up as usual. The crude product is purified by column chromatography using mixtures of hexanes/ethyl acetate to afford the pure product. Often, the product will be obtained as a mixture of N-protected and N-deprotected beta lactams.

In another aspect of the invention, and as illustrated in Reaction 14, a beta lactam with oxygen substitution on the ring nitrogen is converted to the corresponding beta-lactam with hydrogen substitution on the ring nitrogen.

Reaction 14

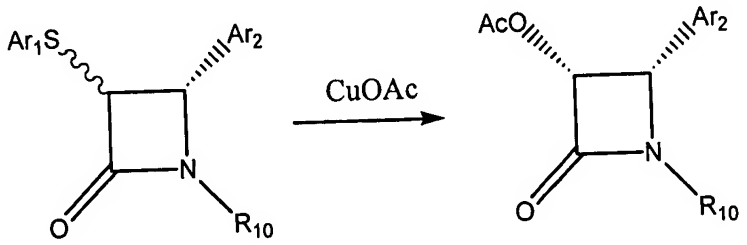


More specifically, a beta lactam with oxygen substitution on the ring nitrogen is dissolved in methanol at room temperature and treated with $Pd(OH)_2$-C

(or any other reducing agent) and the resulting suspension is stirred under hydrogen atmosphere for overnight. The reaction mixture is filtered through a pad of celite and the volatile component(s) of the filtrate are evaporated. The residue was dissolved in dichloromethane and worked up as usual. The crude product is purified by column chromatography using mixtures of hexanes/ethyl acetate to afford the pure beta lactam.

In another aspect, the present invention provides a process comprising the process disclosed in Reaction 15, wherein a thioaryl group is converted to a protected hydroxyl group

Reaction 15



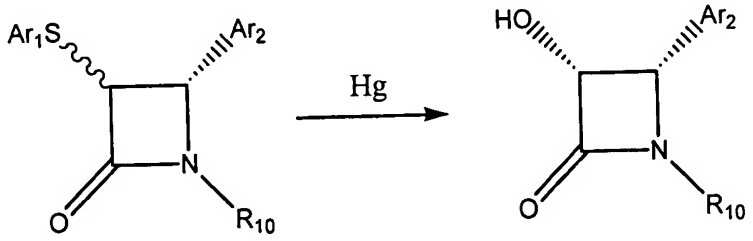
wherein Ar_1 and Ar_2 are independently selected from alkyl, alkenyl, alkynyl, aryl or substituted aryl radical; and R_{10} is hydrogen, C_1-C_6alkyl, aryl or substituted aryl radical; wherein a substituted aryl radical is substituted with one or more of halogen, hydroxyl, alkoxy, aryloxy, heteroaryloxy, amino, alkylamino, dialkylamino, mercapto, alkylthio, arylthio, heteroarylthio, cyano, carboxyl, alkoxycarbonyl where the alkoxy portion contains 1 to 15 carbons, aryloxycarbonyl where the aryloxy portion contains 6 to 20 carbon, or heteroarylcarbonyl where the heteroaryl portion contains 3 to 15 carbon atoms.

More specifically, a beta lactam with a phenylthio substitution on the ring is dissolved in an organic solvent at room temperature and treated with copper acetate. The reaction mixture is filtered through a pad of celite and the volatile component(s) of the filtrate are evaporated. The crude product is purified by

column chromatography using mixtures of hexanes/ethyl acetate to afford the pure beta lactam.

In another aspect, the present invention provides a process comprising the process disclosed in Reaction 16 wherein a thioaryl group is converted to a hydroxyl group

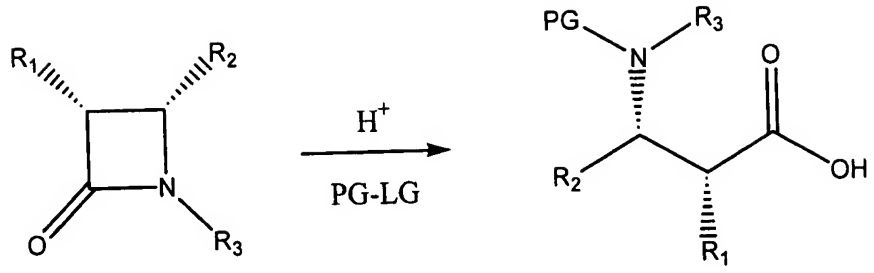
Reaction 16



wherein Hg represents a mercuric reagent, *e.g.*, mercuric oxide or mercuric trifluoroacetate, and Ar_1 and Ar_2 are independently selected from alkyl, alkenyl, alkynyl, aryl or substituted aryl radical; and R_{10} is hydrogen, C_1-C_6alkyl, aryl or substituted aryl radical; wherein a substituted aryl radical is substituted with one or more of halogen, hydroxyl, alkoxy, aryloxy, heteroaryloxy, amino, alkylamino, dialkylamino, mercapto, alkylthio, arylthio, heteroarylthio, cyano, carboxyl, alkoxycarbonyl where the alkoxy portion contains 1 to 15 carbons, aryloxycarbonyl where the aryloxy portion contains 6 to 20 carbon, or heteroarylcarbonyl where the heteroaryl portion contains 3 to 15 carbon atoms. Optionaly, the mercuric reagent may be combined with ceric ammonium nitrate (CAN).

6. Conversion of a beta-lactam compound to a 3-phenylisoserine compound

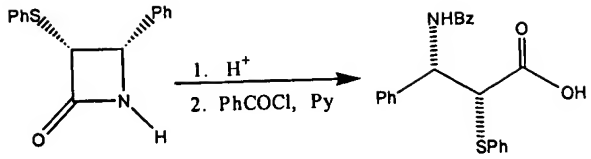
In another aspect, the present invention provides a process of opening a beta-lactam ring. The process may be illustrated by the following scheme



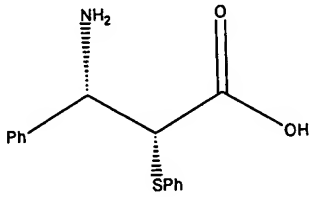
wherein R_1 is hydroxyl, protected hydroxyl, thiol, or protected thiol; LG is a leaving group; PG is an amino protecting group; R_2 is alkyl, alkenyl, alkynyl, or aryl where R_2 is optionally substituted with one or more of halogen, hydroxyl, alkoxy, aryloxy, heteroaryloxy, amino, alkylamino, dialkylamino, mercapto, alkylthio, arylthio, heteroarylthio, cyano, carboxyl, alkoxycarbonyl where the alkoxy portion contains 1 to 15 carbons, aryloxycarbonyl where the aryloxy portion contains 6 to 20 carbon, or heteroarylcarbonyl where the heteroaryl portion contains 3 to 15 carbon atoms; R_3 is hydrogen, C_1-C_6 alkyl or aryl where R_3 is optionally substituted with one or more halogens, hydroxyl, alkoxy, aryloxy, heteroaryloxy, amino, alkylamino, dialkylamino, mercapto, alkylthio, arylthio, heteroarylthio, cyano, carboxyl, alkoxycarbonyl where the alkoxy portion contains 1 to 15 carbons, aryloxycarbonyl where the aryloxy portion contains 6 to 20 carbon, or heteroarylcarbonyl where the heteroaryl portion contains 3 to 15 carbon atoms; and H^+ is a proton source. Optionally, the ring-opened product is purified by column chromatography followed by recrystallization, where the recystallization is preferably performed with an organic solvent. The process may be performed in a mixture of organic solvent and aqueous acid. In a preferred embodiment, R_1 is thiophenyl, R^2 is phenyl, and R^3 is hydrogen.

For example, in one embodiment the present invention provides for the conversion of a β-lactam with thiophenyl substitution to the corresponding phenylisoserine compound as shown in Reaction 17.

Reaction 17



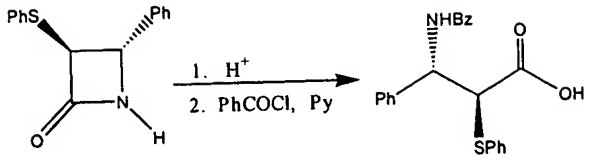
More specifically, a β-lactam is dissolved in a minimum volume of DMSO or mixtures of DMSO/DCM and hydrochloric acid is added. The stirred reaction mixture is heated to about 85°C for ca. 16 hrs. The reaction mixture is cooled to room temperature and dried under vacuum to give a powder, which is the salt of an intermediate compound of the structure



This powder is dissolved in pyridine under an inert atmosphere (*e.g.*, argon) and benzoyl chloride is added dropwise at room temperature. The reaction mixture is stirred at this temperature for about 2 hrs. The reaction mixture is acidified with 0.1N HCl and the crude product is extracted with dichloromethane. The combined organic extracts are dried over anhydrous magnesium sulfate and concentrated *in vacuo* to dryness. The crude product is purified by column chromatography using hexane/ethyl acetate and dichloromethane/ methanol to afford the pure cis phenylisoserine side chain.

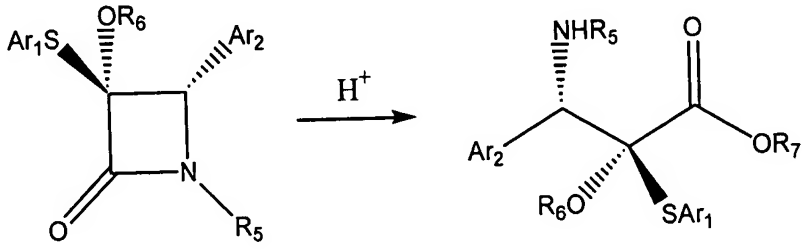
In another aspect of the invention, ring-opening of a β-lactam provides a phenylisoserine compound as illustrated in Reaction 18.

Reaction 18



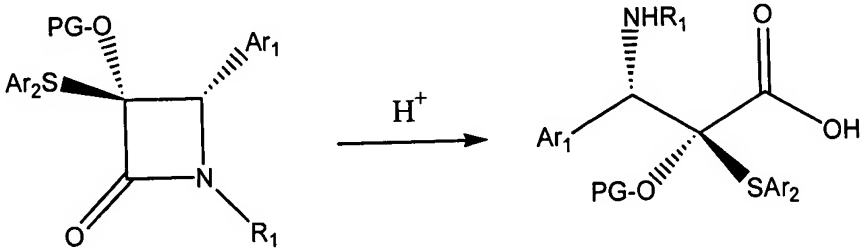
More specifically, treatment of a trans β-lactam with protic acid followed by reaction with benzoyl chloride in base (*e.g.*, pyridine) affords a trans phenylisoserine side chain.

In another aspect, the present invention provides a process wherein a beta-lactam having both thiophenyl and protected hydroxyl substitution is converted to a ring-opened form, as illustrated by the following scheme



wherein Ar_1 and Ar_2 are aryl groups independently selected at each occurrence, R_5 is selected from hydrogen, benzoyl and tBOC, R_6 is a hydroxy protecting group, and R_7 is hydrogen or C_1-C_6alkyl, where R_7 as C_1-C_6alkyl is introduced in an optional esterification reaction. H+ represents a proton source, *e.g.*, mineral acid or organic acid. In one aspect of the invention, Ar_1 and Ar_2 are each phenyl.

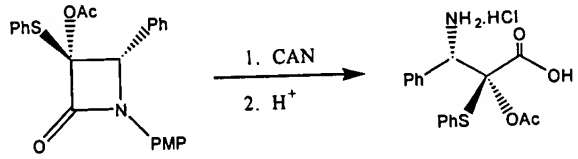
In a separate aspect, the present invention provides a process of opening a beta lactam according to the scheme



wherein PG is a hydroxyl protecting group; Ar_1 and Ar_2 are each aryl groups, where each of Ar_1 and Ar_2 are independently optionally substituted with one or more of halogen, hydroxyl, alkoxy, aryloxy, heteroaryloxy, amino, alkylamino, dialkylamino, mercapto, alkylthio, arylthio, heteroarylthio, cyano, carboxyl, alkoxycarbonyl where the alkoxy portion contains 1 to 15 carbon atoms, and aryloxycarbonyl where the aryloxy portion contains 6 to 20 carbon atoms; and R_1 is hydrogen, alkyl, or –O-PG wherein PG is a protecting group.

For example, in one aspect of the invention, a beta-lactam is ring-opened to afford the corresponding phenylisoserine compound as shown in Reaction 19.

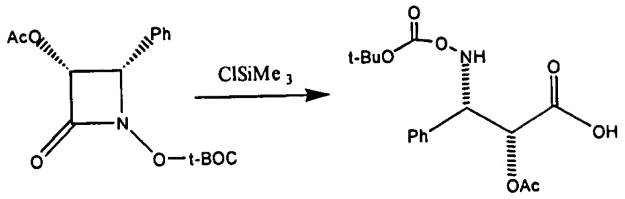
Reaction 19



More specifically, the paramethoxyphenyl (PMP) group of the beta-lactam shown in Reaction 19 is cleaved by using the procedure as in Reaction 7. The product obtained from this cleavage is dissolved in a minimum volume of dichloromethane at room temperature and a solution of hydrochloric acid is added. The stirred solution is heated to about 60°C for about 3 hrs. The reaction mixture is cooled to room temperature and concentrated *in vacuo* to dryness, giving the acid as a powder.

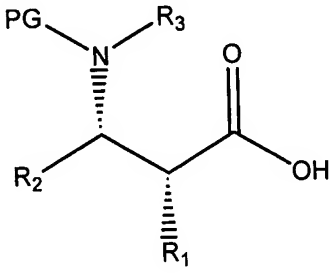
In another aspect, the present invention provides a process whereby a beta lactam having oxygen substitution on the ring nitrogen is converted into a phenylisoserine compound, as illustrated in Reaction 20.

Reaction 20



More specifically, a beta lactam having oxygen substitution on the ring nitrogen is dissolved in dichloromethane at room temperature under argon atmosphere and TMSCl is added. This solution is stirred for about 4 hrs and worked up as usual. The combined organic extracts are dried over anhydrous magnesium sulfate and concentrated *in vacuo* to dryness to give a solid product.

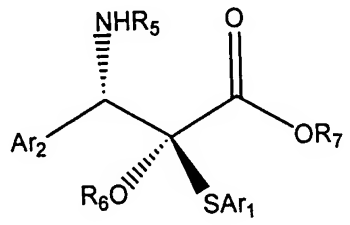
Thus, the present invention generally provides isoserine compound of the formula



wherein R_1 is hydroxyl, protected hydroxyl, thiol, or protected thiol; PG is an amino protecting group; R_2 is alkyl, alkenyl, alkynyl, or aryl where R_2 is optionally substituted with one or more of halogen, hydroxyl, alkoxy, aryloxy, heteroaryloxy, amino, alkylamino, dialkylamino, mercapto, alkylthio, arylthio, heteroarylthio, cyano, carboxyl, alkoxycarbonyl where the alkoxy portion contains 1 to 15 carbons, aryloxycarbonyl where the aryloxy portion contains 6 to 20 carbon, or heteroarylcarbonyl where the heteroaryl portion contains 3 to 15 carbon atoms; R_3 is hydrogen, C_1-C_6 alkyl or aryl where R_3 is optionally substituted with one or more halogens, hydroxyl, alkoxy, aryloxy, heteroaryloxy, amino, alkylamino, dialkylamino, mercapto, alkylthio, arylthio, heteroarylthio, cyano, carboxyl,

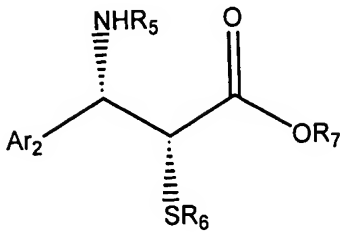
alkoxycarbonyl where the alkoxy portion contains 1 to 15 carbons, aryloxycarbonyl where the aryloxy portion contains 6 to 20 carbon, or heteroarylcarbonyl where the heteroaryl portion contains 3 to 15 carbon atoms; and salts and esters thereof. In one aspect, the isoserine compound is characterized by having R_1 be hydroxyl or protected hydroxyl; R_2 be aryl; and R_3 be hydrogen; including salts and esters thereof. In another aspect, the isoserine compound is characterized by having R_1 be thiol or protected thiol; R_2 be aryl; R_3 be hydrogen; and includes salts and esters thereof.

In addition, the present invention provides compounds of the formula



wherein Ar_1 and Ar_2 are aryl groups independently selected at each occurrence, R_5 is selected from hydrogen, benzoyl and tBOC, R_6 is a hydroxyl protecting group, and R_7 is hydrogen or C_1-C_6alkyl. Optionally, R_6 is selected from methoxymethyl, methoxyethyl, 1-ethoxyethyl, benzyloxymethyl, (beta-trimethylsilyl-ethoxy)methyl, tetrahydropyranyl, 2,2,2-trichloro-ethoxycarbonyl, benzyloxycarbonyl, *tert*-butoxycarbonyl, 9-fluorenylmethoxycarbonyl, 2,2,2-trichloroethoxymethyl, trimethylsilyl, triethylsilyl, tripropylsilyl, dimethylethylsilyl, dimethyl(t-butyl)silyl, diethylmethylsilyl, dimethylphenylsilyl, diphenylmethylsilyl, acetyl, chloroacetyl, dichloroacetyl, trichloroacetyl and trifluoroacetyl.

Furthermore, the present invention provides isoserine compounds of the formula

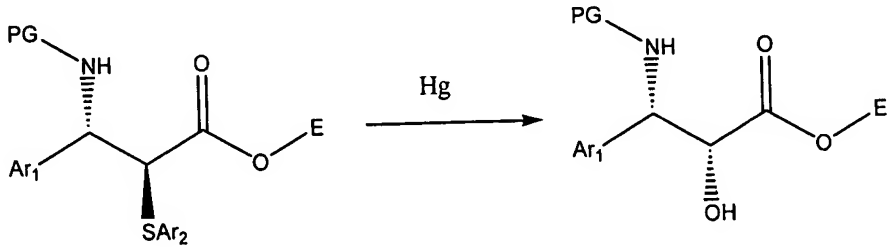


wherein Ar_2 is an aryl group R_5 is selected from hydrogen, benzoyl and tBOC, R_6 is a thiol protecting group, and R_7 is H or C_1-C_6 alkyl. Optionally, the thiol protecting group is triphenylmethyl (trityl, Trt), acetamidomethyl (Acm), benzamidomethyl, 1-ethoxyethyl or benzoyl.

7. Conversion of a 3-phenylisoserine compound to another 3-phenylisoserine compound

In one aspect, the present invention provides a process whereby a thioaryl group in a phenylisoserine compound is replaced with a hydroxyl group, as shown in the following Reaction 21.

Reaction 21

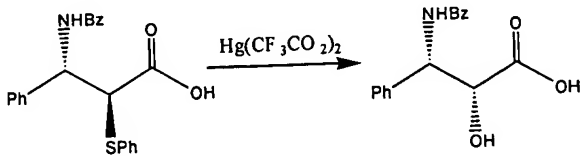


In Reaction 21, PG is an amine protecting group, Ar_1 and Ar_2 are aryl groups, E is hydrogen or an organic group, and Hg represents a mercury-containing oxidizing agent. Optionally, PG is benzoyl or tBOC, and/or E is hydrogen, and/or Ar_1 is

phenyl, and/or Ar_2 is phenyl. Two exemplary mercuric oxidizing agents are HgO and $Hg(CF_3CO_2)_2$.

For example, the present invention provides that a thiophenyl group located at the 2-position of a 3-phenylisoserine may be replaced with a hydroxyl group of the opposite configuration, as shown in Reaction 22.

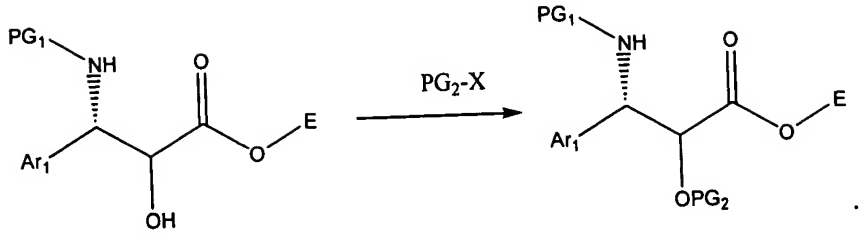
Reaction 22



More specifically, a trans 2-thiophenyl 3-phenylisoserine compound is dissolved in an inert solvent, *e.g.*, freshly distilled THF, under an inert atmosphere, *e.g.*, argon gas, and a mercury-containing oxidizing agent, *e.g.*, mercuric oxide (HgO) or $Hg(CF_3CO_2)_2$ as shown in Reaction 22, is added in one portion at room temperature and the reaction mixture stirred at this temperature for about 72 hrs. The reaction is worked up according to procedures known in the art for reactions with mercuric oxidizing agent, and the product is purified by column chromatography using mixtures of acetone/methanol to afford the pure cis phenylisoserine side chain.

In another aspect, the present invention provides a process whereby a hydroxyl group in a phenylisoserine compound is converted to a protected hydroxyl group, as shown in Reaction 23.

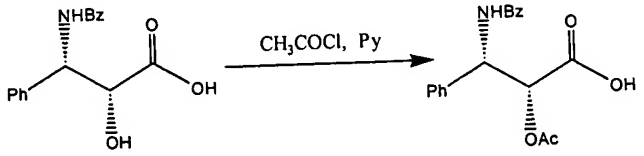
Reaction 23



In Reaction 23, PG_1 is an amine protecting group, Ar_1 and Ar_2 are aryl groups, E is hydrogen or an organic group, PG_2 is a hydroxyl protecting group, and PG_2-X represents a reagent that introduces a protecting group onto a hydroxyl group. Optionally, PG_1 is benzoyl or tBOC, and/or E is hydrogen, and/or Ar_1 is phenyl, and/or Ar_2 is phenyl and/or PG_2 is acetyl. An exemplary reagent to add a protecting group onto a hydroxyl group is acetyl chloride. Other reagents are well known in the art, including those set forth in T. W. Greene and P. G. M. Wuts, "Protective Groups in Organic Synthesis," Second Edition, John Wiley and Sons, New York, N.Y., 1991, Chapters 2 and 3.

For example, the present invention provides for the acylation of the 2-hydroxy group of a 3-phenyl-2-hydroxy isoserine compound, as shown in Reaction 24.

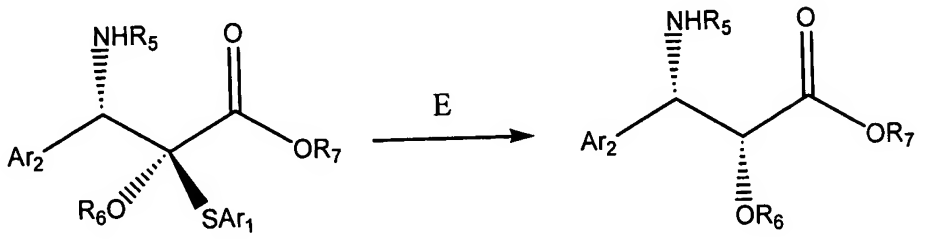
Reaction 24



More specifically, a cis phenylisoserine compound is dissolved in a basic solvent, *e.g.*, pyridine, under an inert atmosphere, *e.g.*, argon gas, at about room temperature and acetyl chloride is added dropwise to the stirred solution. The solution is stirred for about 30 minutes and worked up according to methods known in the art for acylation reaction. The crude product is purified by column

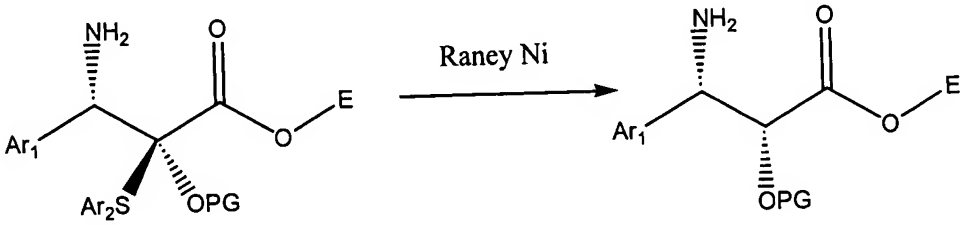
chromatography using mixtures of dichloromethane/methanol to afford the pure acetylated cis phenylisoserine side chain acid.

In another aspect, the present invention provides a process whereby a thioaryl group is removed from an arylisoserine compound, as illustrated by the scheme



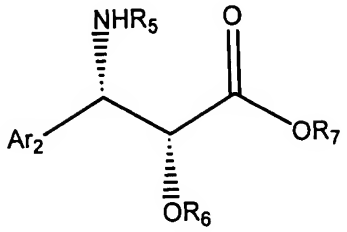
wherein Ar_1 and Ar_2 are aryl groups independently selected at each occurrence, R_5 is selected from hydrogen, benzoyl and tBOC, R_6 is C_1-C_6 alkyl, R_7 is H or C_1-C_6 alkyl, and E represents a desulfuration reagent. Raney nickel is a suitable desulfurization reagent. In a preferred embodiment, each of Ar_1 and Ar_2 is phenyl. For example, the present invention provides a process whereby a thioaryl group is removed from an arylisoserine compound as illustrated by the scheme of Reaction 25.

Reaction 25



In the above scheme, Ar_1 and Ar_2 are aryl groups, E is hydrogen or an organic group, and OPG represents a protected hydroxyl group. Optionally, Ar_1 is phenyl, and/or Ar_2 is phenyl, and/or E is hydrogen and/or PG is acetyl or ethoxyethyl (EE).

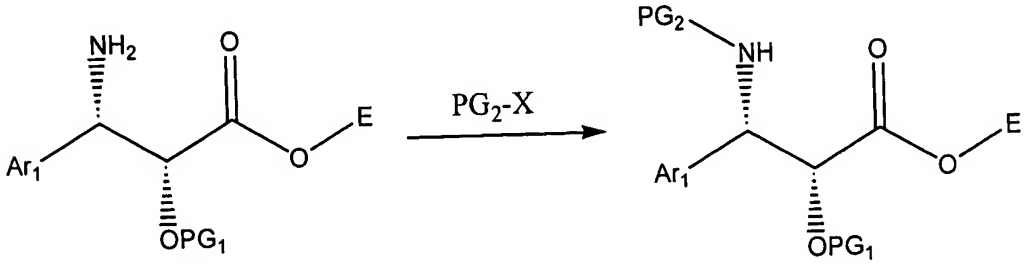
Thus, the present invention provides compounds of the formula



wherein Ar_2 is an aryl group R_5 is selected from hydrogen, benzoyl and tBOC, R_6 is a hydroxyl protecting group, and R_7 is H or C_1-C_6 alkyl. Optionally, R_6 is selected from methoxymethyl, methoxyethyl, 1-ethoxyethyl, benzyloxymethyl, (beta-trimethylsilyl-ethoxy)methyl, tetrahydropyranyl, 2,2,2-trichloro-ethoxycarbonyl, benzyloxycarbonyl, *tert*-butoxycarbonyl, 9-fluorenylmethoxycarbonyl, 2,2,2-trichloroethoxymethyl, trimethylsilyl, triethylsilyl, tripropylsilyl, dimethylethylsilyl, dimethyl(t-butyl)silyl, diethylmethylsilyl, dimethylphenylsilyl, diphenylmethylsilyl, acetyl, chloroacetyl, dichloroacetyl, trichloroacetyl and trifluoroacetyl.

In another aspect, the present invention provides a process whereby a protecting group is added to the amino group of an arylisoserine compound, as illustrated in the scheme of Reaction 26.

Reaction 26

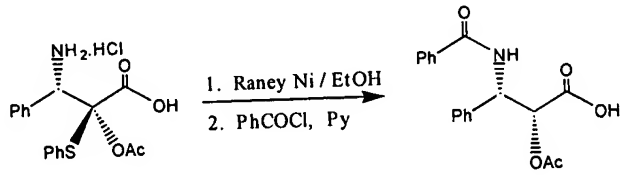


In Reaction 26, Ar_1 and Ar_2 are aryl groups, E is hydrogen or an organic group, PG_1 represents a hydroxyl protecting group and PG2 represents an amine protecting group. Optionally, Ar_1 is phenyl, and/or Ar_2 is phenyl, and/or E is hydrogen and/or PG_1 is acetyl. Optionally, when paclitaxel is the target taxane,

PG_2 is a benzoyl group. However, when taxotere is the target taxane, then PG_2 is a tBOC group.

In another aspect of the present invention, a protecting group is added to the amine group of a 3-arylisoserine compound, and a thioaryl group is removed from the alpha carbon, as illustrated in Reaction 27, where phenyl is shown as a representative aryl group, acetate is shown as a representative hydroxyl protecting group, and benzoyl is shown as a representative amine protecting group.

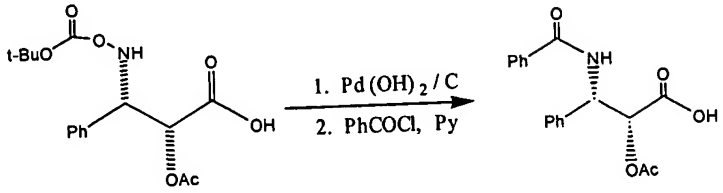
Reaction 27



More specifically, a phenylisoserine compound is dissolved in ethanol at room temperature and Raney nickel is added in one portion to the stirred solution and the reaction mixture is stirred at this temperature for 3 hrs. The reaction mixture is filtered and the filtrate is evaporated. The residue is dissolved in dichloromethane and worked up as usual. This resulting solid is dissolved in pyridine under argon atmosphere and benzoyl chloride added dropwise at room temperature. The reaction mixture is stirred at this temperature for about 4 hrs. The reaction mixture is acidified with 0.1N HCl and the crude product is extracted with dichloromethane. The combined organic extracts are dried over anhydrous magnesium sulfate and concentrated *in vacuo* to dryness. The crude product is purified by column chromatography using dichloromethane/methanol to afford the pure cis 2'-acetylated phenylisoserine side chain. When taxotere is the target taxane, a reagent that adds a tBOC group to an amine group may be used in lieu of benzoyl chloride.

In another aspect of the invention, the protecting group on the nitrogen atom of a 3-phenylisoserine compound is replaced with a different protecting group as illustrated in Reaction 28.

Reaction 28



Here, a O-t-BOC protected phenylisoserine compound is treated under reducing conditions as shown in reaction 28, and then benzoylated using benzoyl chloride in pyridine according to reaction 27 to give the 2'-protected phenylisoserine taxol side chain.

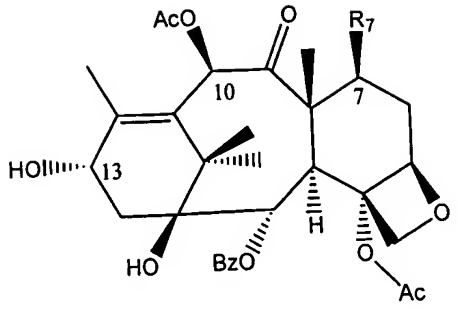
8. Combinations of Reactions

The various reactions described in this section may be carried out sequentially, so long as the product of one reaction may be used as the starting material of another reaction. Each of these possible combinations is a separate aspect of the present invention. Exemplary reaction sequences are shown in Figures 1-3.

C. Baccatin III Compounds

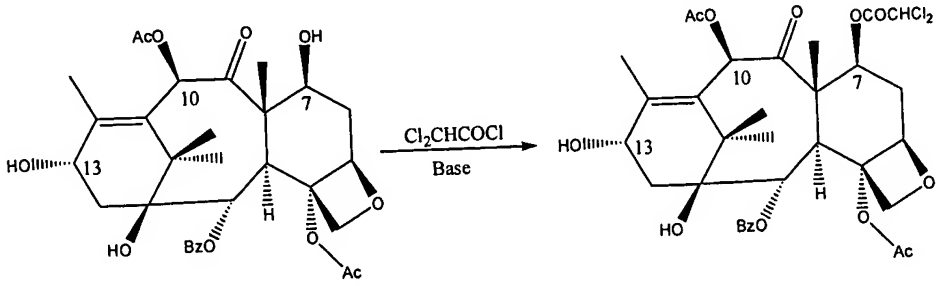
C7-dichloroacetyl baccatin III

In one aspect the present invention provides C7-dichloroacetyl baccatin III of the following formula (R_7 = -OCOCHCl$_2$).



This compound is a useful intermediate in the production of taxanes. This compound may be prepared according to Reaction 29, which is another aspect of the present invention.

Reaction 29

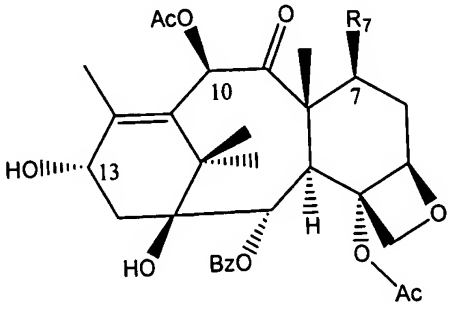


In Reaction 29, the base may be an amine base, *e.g.*, dimethylaminopyridine (DMAP). The reaction is typically conducted in an inert solvent, *e.g.*, dichloromethane (DCM). For example, Baccatin III may be dissolved in anhydrous dichloromethane under an argon atmosphere at room temperature. To this solution is added DMAP followed by dichloroacetyl chloride. The mixture is left at room temperature for overnight. The mixture is then quenched with cold water and extracted thrice with dichloromethane. The organic layer is washed with water and than with brine to remove unwanted salts. The organic layer may then be dried and evaporated under vacuum, and the residue recrystallized or column chromatographed with dichloromethane/ethyl acetate mixtures to afford C7 protected baccatin III.

Alternatively, the C7 protected baccatin III or C7 and C10 protected baccatin III can also be prepared from 10 DAB or 9DHB (9-dihydro-13-acetylbaccatin III) in a similar manner.

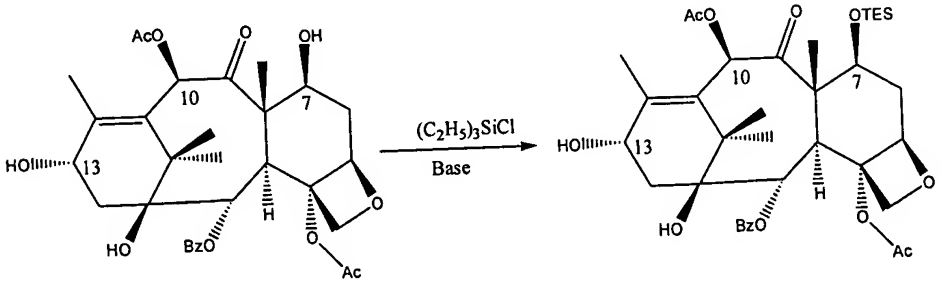
C7-triethylsilyl baccatin III

In one aspect the present invention provides C7-triethylsilyl baccatin III of the following formula (R_7 = -O-Si(CH_2CH_3)$_3$).



This compound is a useful intermediate in the production of taxanes. This compound may be prepared according to Reaction 30, which is another aspect of the present invention.

Reaction 30

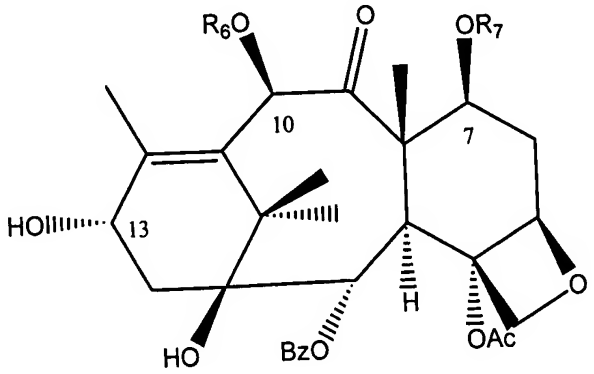


In Reaction 30, the base may be an amine base, *e.g.*, dimethylaminopyridine (DMAP) or pyridine. The reaction is typically conducted in an inert solvent, *e.g.*, dichloromethane (DCM). For example, Baccatin III may be dissolved in anhydrous dichloromethane under an argon atmosphere at room

temperature. To this solution is added pyridine followed by triethylsilyl chloride. The mixture is left at room temperature for overnight. The mixture is then quenched with cold water and extracted thrice with dichloromethane. The organic layer is washed with water and than with brine to remove unwanted salts. The organic layer may then be dried and evaporated under vacuum, and the residue recrystallized or column chromatographed with dichloromethane/ethyl acetate mixtures to afford C7 protected baccatin III.

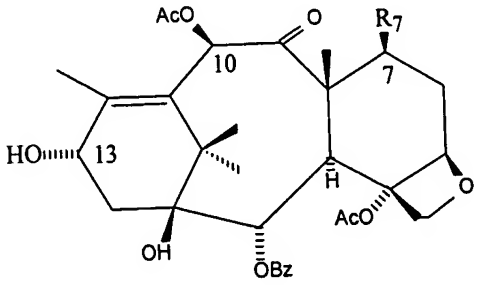
D. Condensation of the C7 Protected Baccatin III with the Side Chain

In another aspect, the present invention provides for the coupling of a sidechain as described in the previous section, which may be either a beta lactam or a phenylisoserine, with a baccatin-type compound. In general, the baccatin-type compound is described by the formula



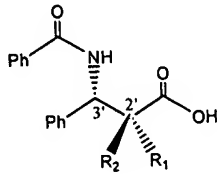
wherein R_6 and R_7 are selected from hydrogen and hydroxy protecting groups. The sidechain couples to the baccatin-type compound at the hydroxyl group located at C13 of the baccatin-type compound. In various exemplary embodiments of the invention: R_6 is acetyl and R_7 is triethylsily (TES); R_6 is acetyl and R_7 is $-COCHCl_2$; R_6 is dichloroacetyl and R_7 is triethylsily (TES); or R_6 is dichloroacetyl and R_7 is $-COCHCl_2$. In a preferred embodiment, the coupling is performed in the presence of a dialkylcarbodiimide, *e.g.*, dicyclohexylcarbodiimide.

In one embodiment, a di-chloroacetyl baccatin III (R_7 = -OCOCHCl$_2$) or triethylsilyl (TES) baccatin III (R_7 = TES) of the following formula (I"):

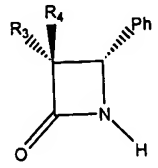


(I")

is reacted with an N-CBz C2'-protected 3-phenylisoserine side chain of the following formula (IIa"), or with a β-lactam of the following formula (IIb"):

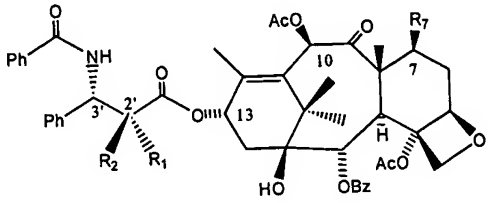


(IIa")

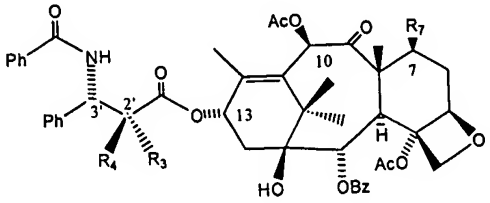


(IIb")

to form an intermediate of the following formulas (III") or (IV"):



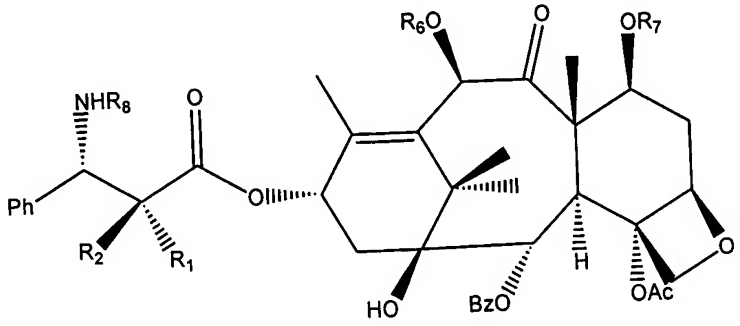
(III")



(IV")

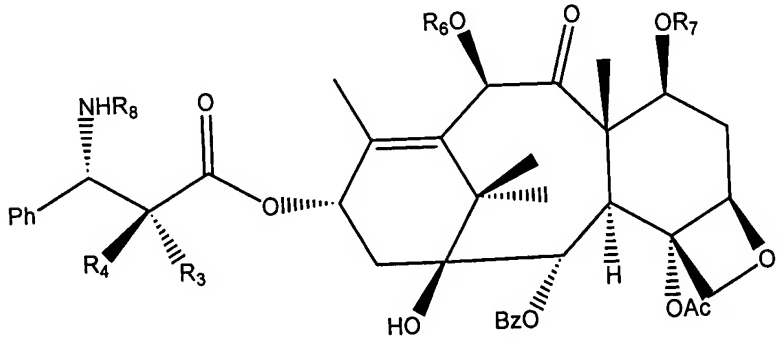
In another embodiment, the intermediate of formula (III") or (IV") is further modified to yield paclitaxel or analogs thereof. For example, the R_7 group at the C7 position and the R group at the C2' site may be converted to hydroxyl groups to yield paclitaxel. In one embodiment of the invention, these coupling reactions are accomplished under the influence of a dialkylcarbodiimide, *e.g.*, DCC.

In general, reaction of a beta lactam (see, *e.g.*, Reactions 6, 8, 9, 12, and 13) or a phenylisoserine side chain (see, *e.g.*, Reactions 10, 11, 18, 20, 22 and 24) may be accomplished by reacting with a C7 protected baccatin III (Schemes I and II below) to yield an intermediate of the following formula (IIIa") or (IIIb") or (IVa") or (IVb"):



(IIIa" and IIIb")

wherein R_6 is acetyl, R_7 is a hydroxy protecting group, and R_8 is benzoyl (compound IIIa") or t-BOC (compound IIIb"); and

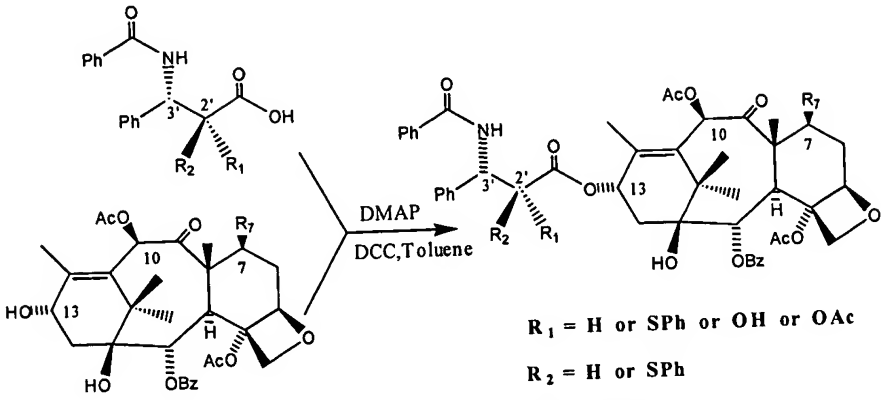


(IVa" and IVb")

wherein R_6 is acetyl, R_7 is a hydroxy protecting group, and R_8 is benzoyl (compound IVa") or t-BOC (compound IVb").

Such reaction between compounds of formulas (I") and those of formulas (IIa") and (IIb") may be accomplished as illustrated in following reaction Schemes.

Scheme 1

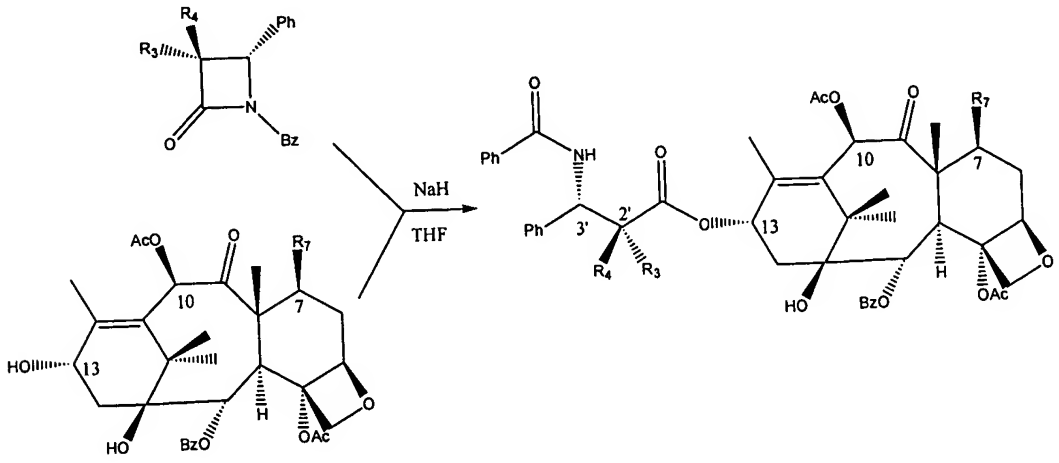


Here, the side chain acid of formula IIa" (obtained as described previously) is dissolved in anhydrous toluene under argon atmosphere at room temperature. To this stirred solution of the side chain acid is added sequentially DCC, DMAP and the C7 protected baccatin III of formula I". The resulting mixture is then heated at about 75°C for 16 hrs. It should be noted that any other dialkycarbodiimides may be substituted for the dicyclohexylcarbodiimide (DCC), with one example being diisopropylcarbodiimide. The solution is then allowed to cool to room temperature, and next an equal volume of dichloromethane is added. The combined organics are then washed with cold dilute hydrochloric acid solution, water, and finally brine. The organic layer is separated, dried, and reduced under vacuum. The resulting residue is purified by column chromatography using mixtures of dichloromethane/ethyl acetate or hexanes/ethyl acetate to afford the pure coupled intermediate taxane of formula III" or IV".

The process illustrated by Scheme 1 is suited for the preparation of paclitaxel since the sidechain amino group is protected with a benzoyl group. In

another embodiment of the invention (not illustrated) the process of Scheme 1 is performed with a sidechain having a t-BOC protecting group for the sidechain amino group, where this embodiment is well-suited for the preparation of taxotere.

Scheme 2



In Scheme 2, in preferred embodiments, R^3 is H, SPh, OH, OAc or ethoxyethyl, R^4 is H or SPh, and R^7 is O-TES or $OCOCHCl_2$. Here, the beta lactam of formula IIb" (obtained as described previously) and the C7 protected baccatin III is dissolved in anhydrous freshly distilled THF under argon atmosphere at room temperature. This stirred solution is cooled to 0°C and added to a suspension of NaH in THF at 0°C. The solution is warmed slowly to room temperature and maintained at this temperature for 3 hrs. The reaction mixture was cooled to 0°C and quenched with brine. The reaction mixture was extracted with dichloromethane and the combined extracts were washed several times with brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure to give the crude product. The crude product was purified by column chromatography using mixtures of hexanes/ethyl acetate to afford the pure coupled intermediate taxane of formula III" or IV" that could be converted to taxol or its analogs. Although this reaction is illustrated with sodium hydride, in other aspects of the invention the coupling is performed in the presence of a metal base

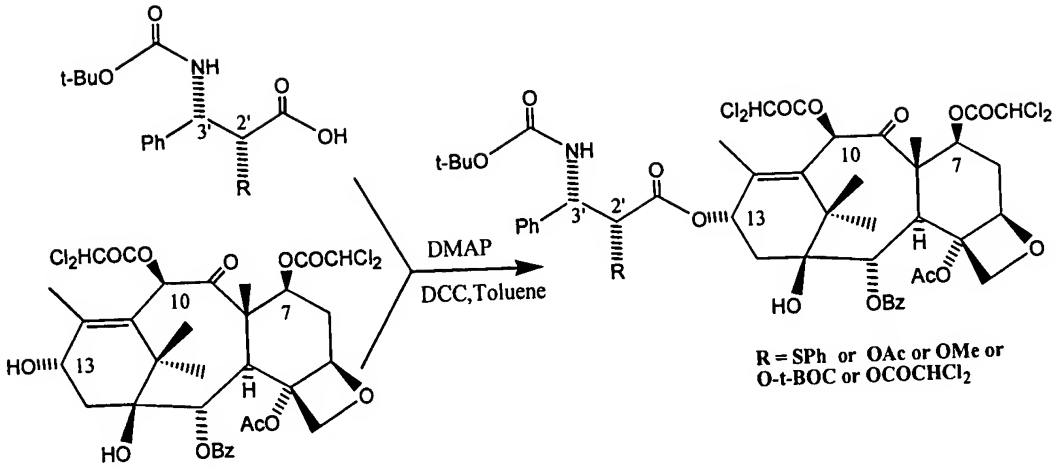
salts, *e.g.*, a metal hexamethyldisilazide (e.g., LiHMDS, NaHMDS, KHMDS), or a Lewis acid, *e.g.*, boron trifluoride etherate.

The process illustrated by Scheme 2 is suited for the preparation of paclitaxel since the nitrogen atom of the beta-lactam is protected with a benzoyl (Bz) group. In another embodiment of the invention (not illustrated) the process of Scheme 2 is performed with the nitrogen atom of the beta-lactam being protected by a t-BOC protecting group, where this embodiment is well-suited for the preparation of taxotere.

Additional examples of the coupling of a sidechain to a baccatin-type compound are shown in the following Schemes 3 and 4. Each of Schemes 3 and 4 is a separate aspect of the present invention. In these schemes "R" represents hydrogen or an organic group, *e.g.*, R may be hydroxyl, protected hydroxyl, thiol, or protected thiol; alternatively R may be alkyl, alkenyl, alkynyl or aryl, where R may be optionally substituted with one or more of halogen, hydroxyl, alkoxy, aryloxy, heteroaryloxy, amino, alkylamino, dialkylamino, mercapto, alkylthio, arylthio, heteroarylthio, cyano, carboxyl, alkoxycarbonyl where the alkoxy portion contains 1 to 15 carbons, aryloxycarbonyl where the aryloxy portion contains 6 to 20 carbon, or heteroarylcarbonyl where the heteroaryl portion contains 3 to 15 carbon atoms. Preferably, "R" is selected as appropriate for the preparation of paclitaxel or taxotere. DCC is shown as the coupling reagent in Schemes 3 and 4 for illustrative purpoes, however, other dialkylcarbodiimides may be used in lieu of, or in combination with, dicyclohexylcarbodiimide (DCC).

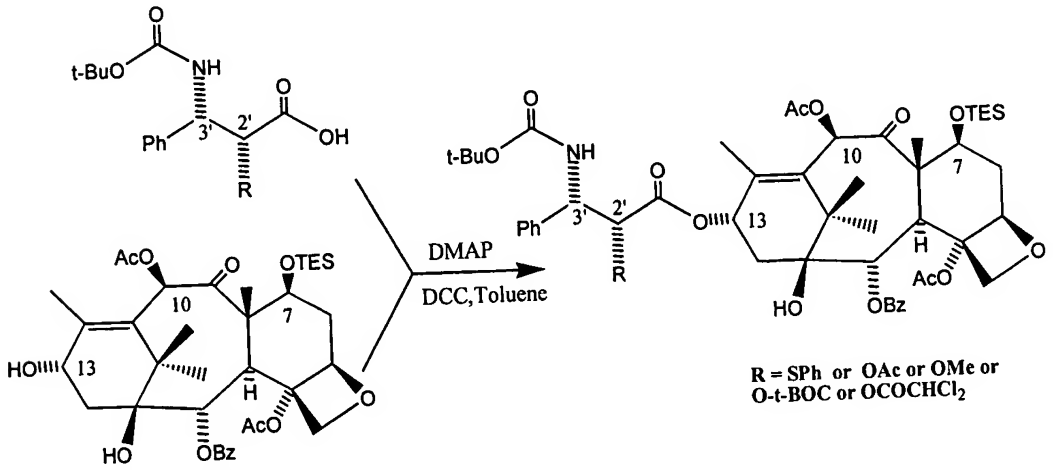
Scheme 3

I



C7, C10-bis(dichloroacetyl)10DAB

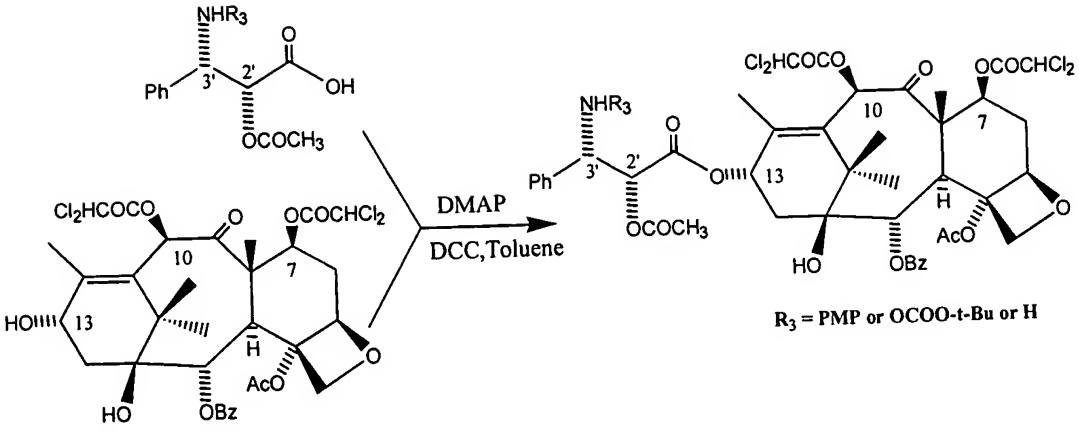
II



C7, triethylsilyl baccatin III

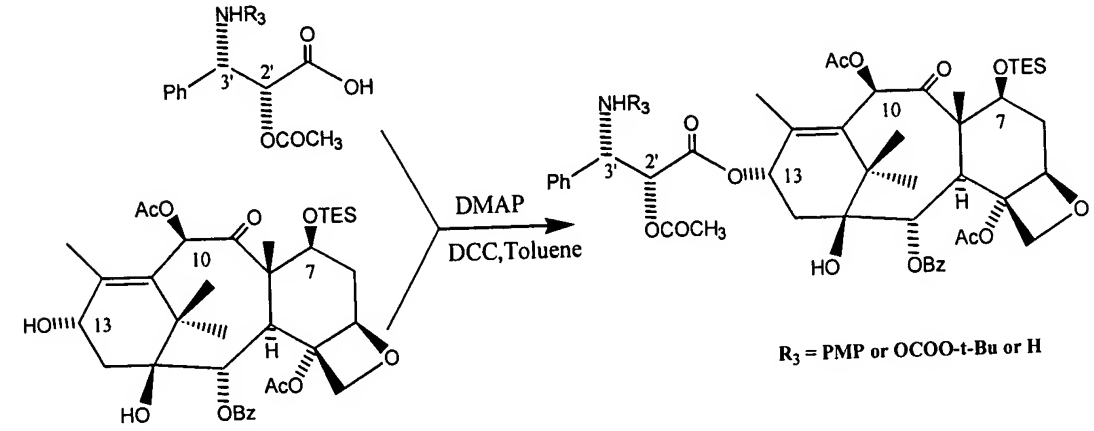
Scheme 4

I



C7, C10-bis(dichloroacetyl)10DAB

II



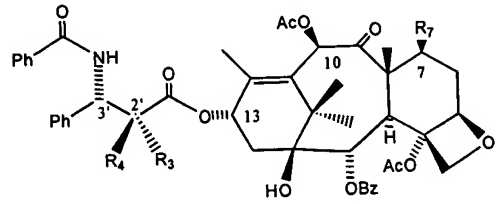
C7, triethylsilyl baccatin III

E. Conversion of the compound of formula III or IV to paclitaxel, taxotere, or an analog thereof

Following synthesis of compounds of formula III" or IV", the same may then be used as an intermediate for the preparation of paclitaxel, taxotere, or analogs thereof. For example, the following Scheme 5 illustrates hydrolysis of the

C2'-protected groups and C7-dichloroacetyl or TES to form paclitaxel under mild conditions, thus not disturbing the ester linkage and various substituents.

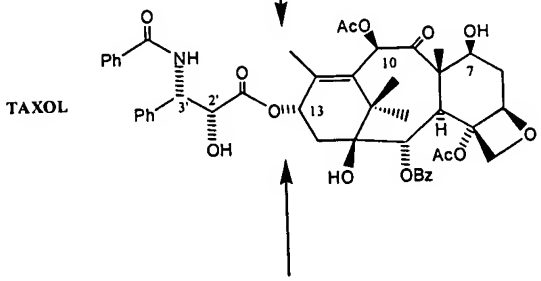
Scheme 5



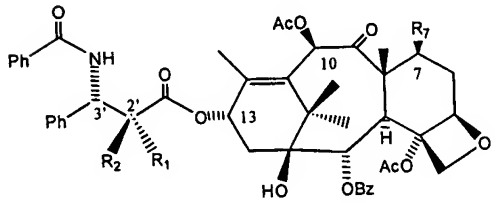
R_3 = H or SPh or OH or OAc

R_4 = H or SPh

R_7 = OTES or $OCOCHCl_2$



TAXOL



R_1 = H or SPh or OH or OAc

R_2 = H or SPh

R_7 = OTES or $OCOCHCl_2$

Here, the C2' protected groups and the C7 protected groups can be removed to give taxol or its analogs. An analogous process of the present invention for the preparation of taxotere is shown in Figures 4 and 5.

All of the above U.S. patents, U.S. patent application publications, U.S. patent applications, foreign patents, foreign patent applications and non-patent publications referred to in this specification and/or listed in the Application Data Sheet, are incorporated herein by reference, in their entirety.

From the foregoing it will be appreciated that, although specific embodiments of the invention have been described herein for purposes of illustration, various modifications may be made without deviating from the spirit and scope of the invention. Accordingly, the invention is not limited except as by the appended claims.